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Effects of environmental pH, sodium concentration, and temperature on the spontaneous motility of isolated human uterine muscle

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ONE of the classic methods for studying the physiology of smooth muscle has been to observe the effects of various stimuli on the contractile patterns of isolated muscle strips suspended in a saline bath of suitable composition.[1, 2] During the past several years, we have utilized this technique,[3-6] as have others,[7-11] in an endeavor to obtain a better understanding of the contractile potential of the human uterine musculature.

In an earlier report from these laboratories[12] we have shown that the spontaneous motility displayed by isolated human myometrial tissues is not influenced by such factors as race, previous pregnancies, pregnancy itself, or the presence of benign neoplasia if not included in the excised samplings. Furthermore, the influence of the various phases of the menstrual cycle was found to be minimal, since the rate of contraction recorded from muscle strips obtained from uteri with secretory endometria differed from that ob-

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tained during the proliferative phase at only the 5 per cent confidence level. On the other hand, both frequency and height of contraction were found to be altered by the chronologic age of the donor. The capacity of the muscle strip to shorten decreases, and the frequency of contraction increases with advancing age.

In the present study we have attempted to assay the possible effects of certain variables which may be present in any experiment performed in vitro where of necessity the tissues are exposed to an artificial environment. To this end, the hydrogen ion concentration, sodium content, and temperature of the media surrounding the tissue samples were selected as those factors which might be most variable and which could be expected to affect the motility of the myometrial strips to a significant degree. It was, moreover, considered that since alterations in blood pH, sodium concentration, and temperature occur clinically, an inquiry into their possible effects upon the human myometrium might prove of interest.

Methods

In order to assure optimal motility of the muscle strips employed, only those excised from uteri of women below the age of 47 years were utilized in this study.[12] Since such material is not plentiful, the possibility of using several myometrial strips from each of the available uteri was explored. It was found that a sample of myometrium placed in Locke's solution and maintained at 4° C.[13] for as long as 76 hours usually displayed a motility pattern indistinguishable from that recorded from strips removed from the same uterus, but studied within minutes of their excision. The utility of this observation to the experimentalist is obvious.

All tissues were uniformly suspended within a chamber of 50 ml. capacity and so arranged as to actuate a light, standardized ink-writing lever held by gravity, alone, against a continuously recording kymograph revolving at a rate of 2.5 cm. per minute. Rate of contraction was expressed as the average fraction of a complete contraction-relaxation wave occurring within one minute, while the height of contraction was expressed as the average height in millimeters of the contraction waves as they appeared on the mechanogram. Since the recording system was kept uniform throughout, it was considered that this method of mensuration could be accepted as a valid index for assaying muscle motility under the various experimental conditions imposed.

The pH of the Locke's solution bathing the tissues was altered by varying the carbon dioxide content of the aerating gas or by adding suitable amounts of either hydrochloric acid or sodium hydroxide to the tissue chamber. To permit simultaneous recordings of both uterine activity and pH, the remote electrodes of a Beckman meter were placed directly within the muscle bath. The meter was calibrated with standard buffer solutions and all determinations were made at 37° C.

The concentration of sodium ions within the tissue chamber was reduced in a stepwise

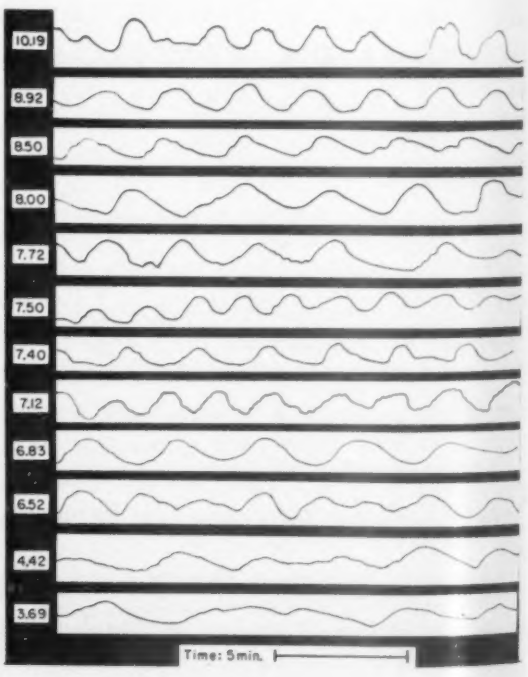


Fig. 1. Spontaneous motility of isolated sections of human myometrial tissue at various environmental hydrogen ion concentrations. That a high degree of contractility may occur over extreme ranges in pH is apparent.

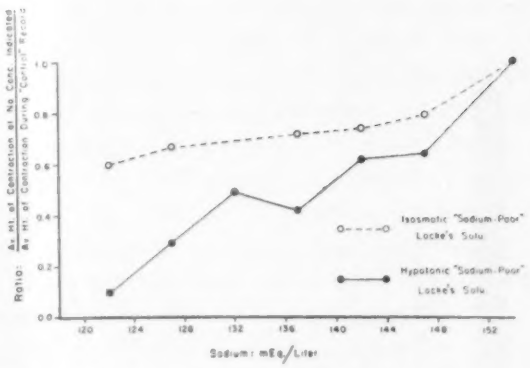


Fig. 2. Effect of reduced sodium concentrations on myometrial activity in an isosmotic environment compared to contractility exhibited in hypotonic solutions of similar sodium content.

fashion by replacing aliquots of the medium with an equal volume of sodium-poor Locke's solution. Since any change in observed muscle motility occurring when the sodium chloride concentration within the bath was thus reduced might be, at least in part, referable to a decrease in osmotic forces, a second series of experiments was carried out. In these, the osmotic pressure of the sodium-poor solution was maintained by replacing the sodium chloride deleted with an isosmotic equivalent of sucrose. Each aliquot withdrawn from the muscle bath was analyzed for sodium concentration by flame photometry and for osmolality by the freezing-point depression technique, using a modified Fiske osmometer. The contractile patterns recorded immediately preceding and following these samplings were accepted as representative of the contractile potential of the muscle strip.

The effects of temperature on uterine activity were observed by lowering that of the outer bath to an average level of 16° C. and permitting the temperature to rise gradually to 46° C. in response to an Aminco heating element during continuous recording of the myometrial response.

Results

Variations in pH of the media surrounding the muscle strips within physiologic or indeed pathologic limits, 7.0 to 8.0, had no demonstrable effect on myometrial activity. Such changes in rhythmicity and height of contraction observed to occur within this range were found by analyses to reflect spontaneous alterations in the contractile pattern, a phenomenon characteristic of smooth muscle, rather than any direct effect of pH. On subjecting the myometrial samples to extremes of hydrogen ion concentrations, above 10.0 or below 4.5 pH units, activity typically ceased. However, even beyond these limits activity continued in 4 of the 26 uterine strips tested.

Fig. 1 illustrates characteristic myometrial activity over a wide range of pH values, and although depressed activity is clearly evident at very low pH levels, some degree of contractility is still apparent. It was concluded that the isolated human myometrium is relatively resistant to changes in the pH of the environment over wide ranges, and that rigid control of environmental pH during in vitro studies on such material is not mandatory within the range 7.0 to 8.0 pH units.

Twenty-eight uterine strips were used to assay the effects of variation in sodium ion concentration on myometrial activity. The concentration of sodium in the medium varied from 118 to 160 mEq. per liter. For statistical purposes each strip served as its own control. Thus, the average height of contraction recorded at each concentration was compared with that obtained for the same tissue while submerged in Locke's solution containing 155 mEq. of sodium per liter and 312 mOsm. per kilogram of water.

Fig. 2 illustrates graphically the effect on the contractile pattern incident to decreasing the concentration of sodium chloride within the environment. It is apparent that decreasing the concentration of sodium chloride within the media was associated with a reduction in myometrial activity. Furthermore, this response was most marked when the osmolality of the bathing fluid as well as the concentration of sodium chloride ions was permitted to decline. These observations suggest that uterine contractility, in vitro, is dependent to a greater extent on the total solute concentration of the surrounding

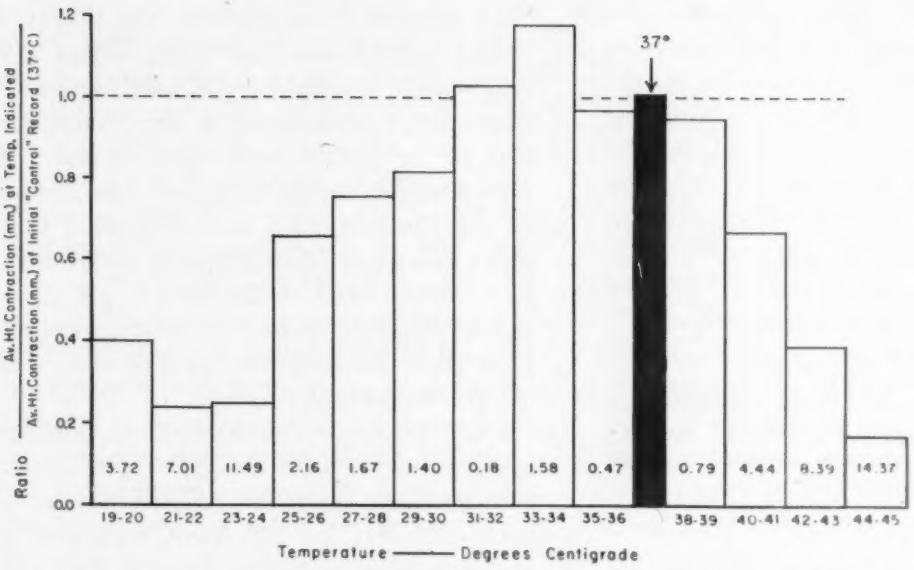


Fig. 3. Effect of alterations in environmental temperature on the motility of isolated human myometrial tissue. No changes of statistical significance were found between 27 and 40° C. The numerical values shown in each rectangle represent the "t" values difference between the mean ratios and unity.

medium than on the specific concentration of sodium and chloride ions per se. They further suggest that the addition of test substances during in vitro studies involving the human myometrium should be performed with circumspection in order to prevent erroneous conclusions.

The effect of alterations in temperature upon myometrial motility was quite characteristic. Abrupt chilling of the tissues from 37 to approximately 16° C. was associated with a tetany-like contraction (increased tone?). On warming, a variable interval of quiescence was observed associated with decreasing "tonus." In all of the strips tested, spontaneous activity reappeared by the time that the environmental temperature reached 24° C. With continued warming, the typical response consisted of an increase in amplitude of contraction with an enhancement of tone. At 37° C. the contractile pattern was characteristically indistinguishable from that recorded during the "control" period. Continued elevation of temperature above 40° C. resulted in a progressive reduction in height of contraction and an acceleration in the rate of activity. Above 46° C. spontaneous activity ceased.

In order to evaluate statistically the effects of alteration of temperature upon the height of myometrial contraction, a series of ratios was established by comparing the average amplitude of the wave forms recorded at each temperature with that observed during the initial "control" period at 37° C. prior to cooling. In Fig. 3 the mean ratios for all of the myometrial samples are shown. In addition, the "t" value (difference between the mean ratios and unity) are depicted. In the temperature range of 27 to 40° C. the height of contraction does not deviate significantly from that recorded for the tissue

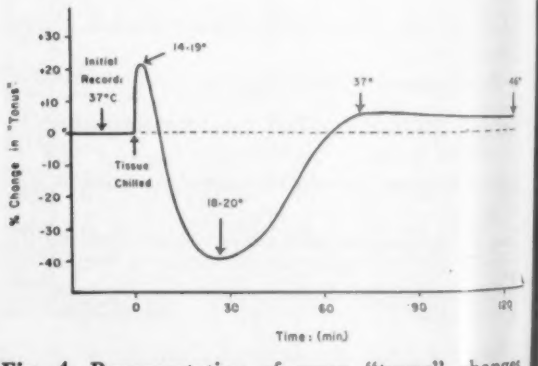


Fig. 4. Representation of mean "tonus" changes with temperature. It was constructed by measuring the average height of the recording stylus from the base line on the kymograph at the end of a contraction-relaxation wave for the range of temperatures shown.

prior to chilling. In Fig. 4, the effect of temperature on "tonus" (height of the recording stylus above the base line during the relaxation phase) is presented in terms of percentage change from initial, "control" tonus. The sudden and marked increase in "tone" on chilling was uniformly followed by an increase in myometrial length as the environmental temperature was raised, being maximal at 18 to 20° C. From this point, "tonus" increased with temperature to a plateau at about 34 to 35° C. Even at 46° C., when contractility ceased, "tonus" approximated that present in the highly active muscle at 37° C.

Comment

The pattern of spontaneous motility exhibited by isolated strips of human myometrial tissue on changes in the physical characteristics of the bathing fluid differs in certain respects from that recorded for other smooth muscle preparations. For example, Evans and Underhill[14] noted that uterine strips obtained from the rabbit, guinea pig, and cat display a substantial increase in tone and rhythmicity in response to raising of the pH of the surrounding media from 7.0 to 8.0, with relaxation and quiescence on reduction of the pH to 6.0. In our experience this range of environmental pH was not associated with any predictable alteration in the activity of human myometrial tissues.

In a like fashion, the damping of activity observed in human uterine muscle samples on reduction of the total solute concentration of the surrounding medium is contrary to the increase in excitability and amplitude of rhythmic movement described for other smooth muscle preparations.[15] McDowall[16] relates that the rat uterus displays a marked enhancement in activity on reduction of the sodium chloride concentration of the medium with maintenance of osmotic pressure by the substitution of isosmotic equivalents of sucrose. A definite diminution in activity was observed to follow this procedure in the case of the human myometrium.

The response of human uterine muscle to changes in environmental temperature also differs in several respects from that reported for other smooth muscles in which chilling is associated with a marked increase in tone with progressive lengthening occurring on warming.[1] Human uterine tissues exhibited an increase in tonus beginning at about 20° C. which continued to approximately 34° C., and did not typically show either the "heat contraction" mentioned by Evans[1] or the marked loss of tone so typical of rabbit smooth muscle (gut) preparations at temperatures above 40° C.[17]

These studies therefore demonstrate that human myometrial tissues respond in certain respects in a different manner to changes in the environment than do other smooth muscle preparations. They further point out the desirability of experimental assurance that conclusions derived from in vitro observations are not influenced by uncontrolled shifts in the environment during physiologic, pathophysiologic, or pharmacologic studies involving the use of such material.

Summary

1. The motility of isolated human myometrial tissue is relatively unaffected by rather wide variations in environmental pH. No statistically significant alterations in either rate or amplitude of contraction were observed between pH 7.0 and 8.0, and one may, therefore, conclude with some confidence that such shifts in hydrogen ion concentration as occur in diseased states can have but negligible effect upon myogenic uterine motility.

2. Reductions in total solute concentration inhibited myometrial activity to a greater degree than a decrease in environmental sodium and chloride ions. It was therefore concluded that the human myometrium is more sensitive to osmotic forces than to concentrations of the above ions.

3. No significant alterations in the motility of human myometrial tissues were observed at environmental temperatures between 27 and 40° C. In all samples tested some degree of activity was present over a temperature range of 24 to 45° C.

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The effect of intravenous estrogens on uterine motility

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THE first report that estrogen was necessary for uterine motility was published in 1925.[5] Since that time considerable experimental work has been done to assess the role of estrogen in the regulation of myometrial activity. These studies have revealed that uterine contractions disappear when animals are castrated and reappear when estrogen is administered.[18] The same findings have been demonstrated in humans.[16, 22, 23] Thus, there seems to be convincing evidence that this hormone plays a major role in the control of myometrial function. Estrogen probably governs uterine muscle function by regulating both the accumulation of its contractile proteins and the activities of the energy-supplying phosphates.[1]

The characteristics of uterine contractions in women with "normal" ovarian function have been rather extensively documented.[7, 14, 17, 22] In fact, a characteristic pattern called the "A wave" pattern has been ascribed to the effects of endogenous estrogen.[6]

The question of whether the human uterus which is under the custody of endogenous estrogen (from ovaries or placenta) would respond to exogenous estrogen has been the subject of numerous studies over the past three decades.[18] Unfortunately, the results from these experiments have been conflicting and inconsistent. One reason for these discrepancies may be that none of these investigations were designed to include three requisites which are now considered to be essential in any in vivo study of the effects of drugs on the dynamics of human myometrium:

1. A tokometric technique should be employed to record the uterine contractions during the study period.

2. The drug under evaluation should be administered under control conditions utilizing placebos, double-blind arrangements, or similar tools of objectivity.

3. The substance under investigation should be given by the intravenous route; in this way the obvious disadvantages of unknown rates of drug absorption and metabolism are minimized.

In the hope that an objective approach might provide an answer to the question of whether exogenous estrogen would influence functioning myometrium, we undertook such a study.

Material and technique

Thirty-three nonpregnant women with no evidence of organic pelvic disease were selected for study. Seven patients were studied in the follicular phase, 9 in the luteal phase, and 5 in the menstrual phase of their cycles; 12 women were investigated during the early postpartum period.

Uterine contractions were recorded by the intrauterine carbon-transducer method developed by Karlson.[9] The transducer probe was inserted into the uterine cavity without cervical dilatation or anesthesia. The spontaneous motility pattern characteristic of the functional state of the uterus was observed

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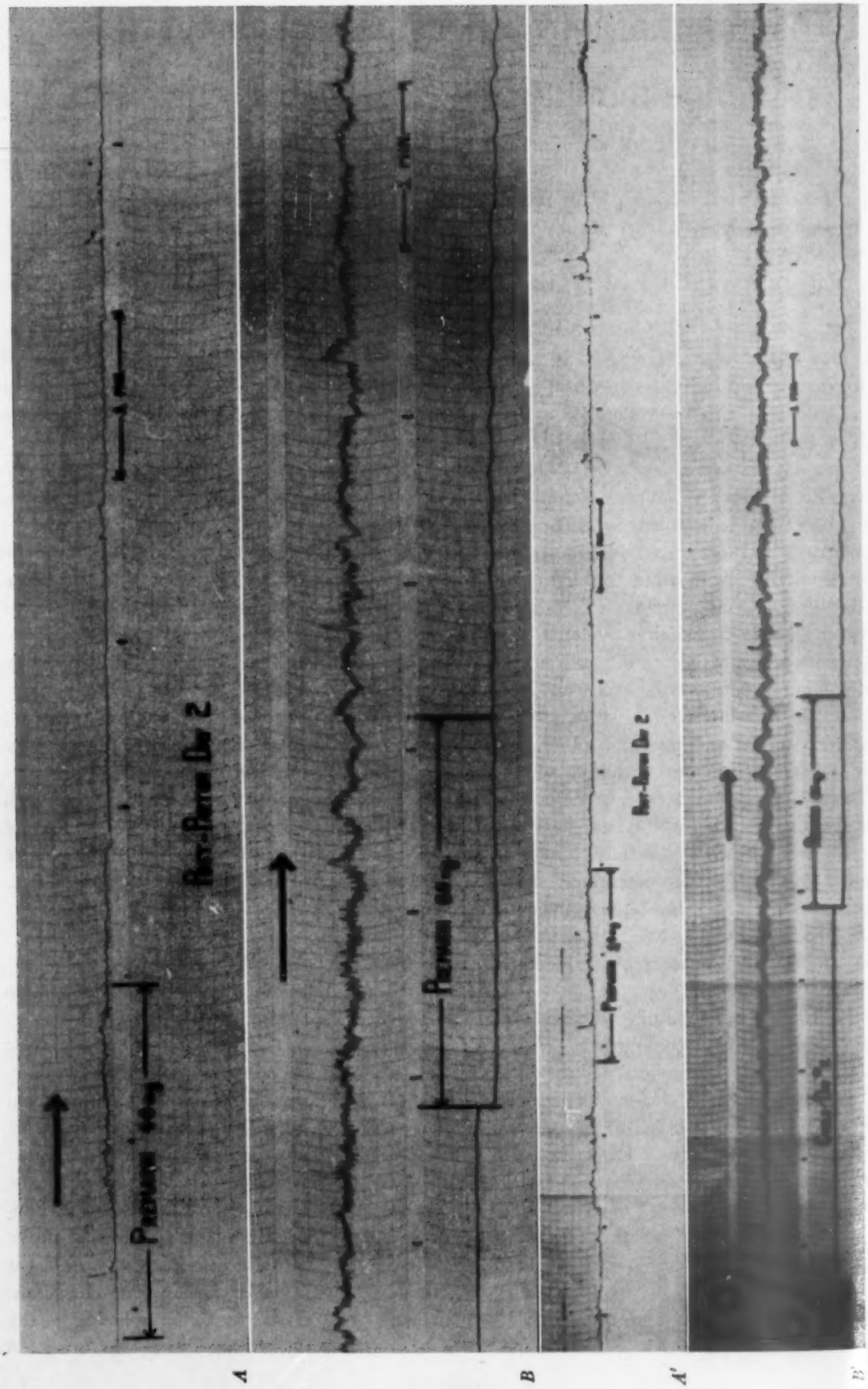


Fig. 1. *A*, *A'*, Postpartum Day 2; Premarin, 40 mg. intravenously. *B*, *B'*, Cycle Day 7; Premarin, 60 mg. intravenously.

for a period of at least 30 minutes. Then an intravenous infusion of 5 per cent glucose in water was started to act as a vehicle for drug injection through its tubing, thus avoiding the disadvantage of repeated dermal puncture. The solution of 5 per cent glucose in water has been shown to have no effect on uterine activity.[19]

Initially, two or three injections of saline were performed through the infusion tubing as controls. Subsequently, conjugated equine estrogens in the form of Premarin* were injected in dosages ranging from 20 to 200 mg. Each injection was given over a period of 20 to 60 seconds. Recordings were continued for periods of approximately 4 hours.

Results

In none of the 33 patients studied was there observed any change in the uterine contraction patterns following administration of the estrogens (Fig. 1). The same was true of saline. This lack of observed effect on uterine dynamics was consistent regardless of the functional state of the uterus, the time of the cycle, or the dosage of estrogens employed. No side effects were noted in any of the women studied.

Comment

The present study has demonstrated that myometrium which is governed by endogenous estrogen does not respond to exogenous estrogens administered in this fashion. More precisely, in patients with "normal" ovarian function, there was no observed effect on motility of the nonpregnant human uteri over the 4 hour period of recording when estrogens were administered by vein in the specified dosages.

It is of interest that this finding of lack of response of the nonpregnant uterus to exogenous estrogens is quite consistent with the ultimate conclusions of similar studies carried out in pregnant patients. In 1953 Jeffcoate and his associates[20] reported that treatment of pregnant patients with estrogen resulted in increased uterine contractions. As a result, these authors recommended the use of estrogen to promote evacuation of the uterus in cases of missed abortions. During the next decade this oxytocic potential of estrogen was observed to be inconsistent by several investigators.[2, 4, 12, 15] In 1950, Jeffcoate himself became suspicious of the uterine-stimulating effect of estrogen[8] and in 1955 his colleagues published a retraction of their original contention.[13] This change of opinion resulted when careful study revealed estrogen to be no more effective for inducing labor than an inert substance. Previously, Karnaky[10] had asserted that intrauterine injection of estrogen actually relaxed a contracted pregnant uterus; also Rowe-Dutton and his group[21] had demonstrated tokometrically that estrogen was ineffective for stimulating uterine evacuation in cases of missed abortion. Thus, the thesis that exogenous estrogen increases the activity of the pregnant uterus seems to have been disproved although it is still occasionally recommended in the literature.[3]

In conclusion, we have presented evidence that the functioning nonpregnant uterus is refractory to estrogen therapy by vein. Speculation as to the reasons for this patriotic allegiance of the myometrium to the estrogens of its gonadal supervisors is indeed tempting. Philosophical discussion, however, should probably be limited to academic ruminations. To wit, there may be a latent period longer than our 4 hour study period before the injected estrogens exert their influence. More likely, when this steroid is given by the intravenous route, it may be deactivated so rapidly by the liver that the uterine muscle has little opportunity to be affected.[11]

Until future studies provide answers to such possibilities, it may be asserted that intravenous estrogens have neither a stimulatory nor an inhibitory influence on the contracting muscle of a nonpregnant uterus.

Summary

1. The role of estrogen in uterine muscle function is briefly reviewed.

*Supplied by Ayerst Laboratories, New York 16, New York.

Fig. 1. *A*, *A'*, Postpartum Day 2; Premarin, 40 mg. intravenously. *B*, *B'*, Cycle Day 7; Premarin, 60 mg. intravenously.

2. Tokometric studies of 33 healthy nonpregnant women were carried out employing an intrauterine carbon transducer.

3. There was no observed change in the uterine contractility patterns of these patients after they were given estrogens intravenously.

4. The impotence of exogenous estrogens on myometrium in both its pregnant and nonpregnant states is discussed.

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Influence of ovarian function on the fibrinolytic enzyme system

I. Ovulatory and anovulatory cycles

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CHANGES in several components concerned with blood coagulation mechanisms have been noted during pregnancy, following administration of exogenous estrogens, and in association with changes in ovarian function. The accumulated evidence suggests that one might anticipate changes in the fibrinolytic enzyme system related to cyclic variations of ovarian steroid production in normal cycles. Likewise, these factors might reflect the unopposed or excessive estrogen production of women with endometrial hyperplasia and anovulatory bleeding. Therefore, the present investigation was undertaken to study the effect of ovarian function on the fibrinolytic enzyme system.

The normal values for prothrombin, proconvertin, plasma thromboplastin component (Factor IX) and fibrinogen are higher in pregnant women[1-6] and a progressive increase in platelet count has also been noted.[7] Profibrinolysin and antifibrinolysin levels increase during pregnancy[6, 8] and these substances as well as fibrinogen can be elevated by administration of synthetic estrogenic compounds to men with prostatic carcinoma.[9-11] Intravenous administration of conjugated estrogens results in increased plasma levels of proaccelerin and prothrombin and in inhibition of antithrombin activity.[12-14] Decreased fibrinogen levels have been noted during menstruation[15] and a cyclic variation in platelets has been reported with maximum counts at midcycle followed by a premenstrual decrease.[16, 17] Clinical observations imply that the state of ovarian function affects bleeding from extrauterine sites. Thus, bleeding from hereditary hemorrhagic telangiectasia noted most frequently just before menstrual periods and after natural or surgical menopause was attributed to a decrease in circulating estrogens and treated successfully with exogenous estrogens.[18, 19] Intravenous administration of conjugated estrogens has been followed by cessation not only of uterine hemorrhage[20] but also of postsurgical, posttraumatic, and "spontaneous" hemorrhage from numerous sites including the ear, nose and throat, gingiva, the gastrointestinal and urinary tracts, the subarachnoid space, and peritoneum.[21-24]

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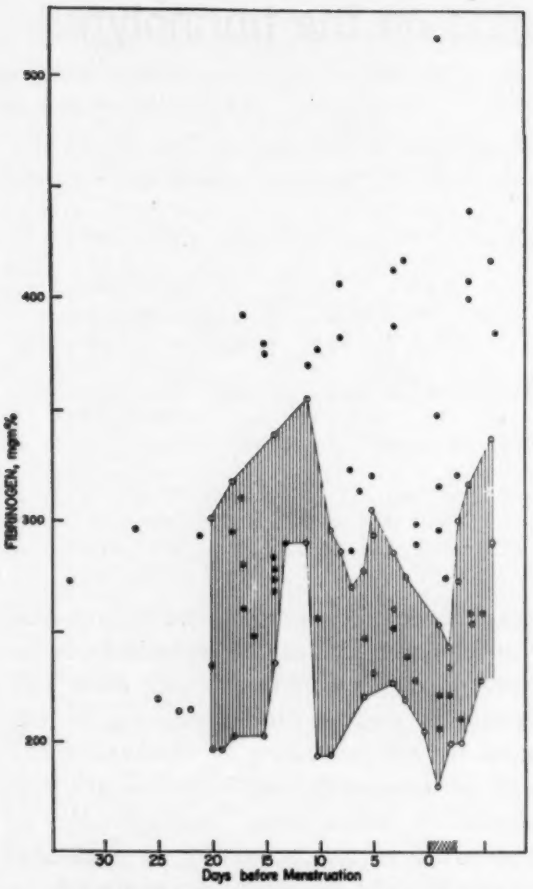


Fig. 1. Composite graph for fibrinogen levels in the ovulatory and anovulatory women. ○ ovulatory women's fibrinogen levels; • anovulatory women's fibrinogen levels.

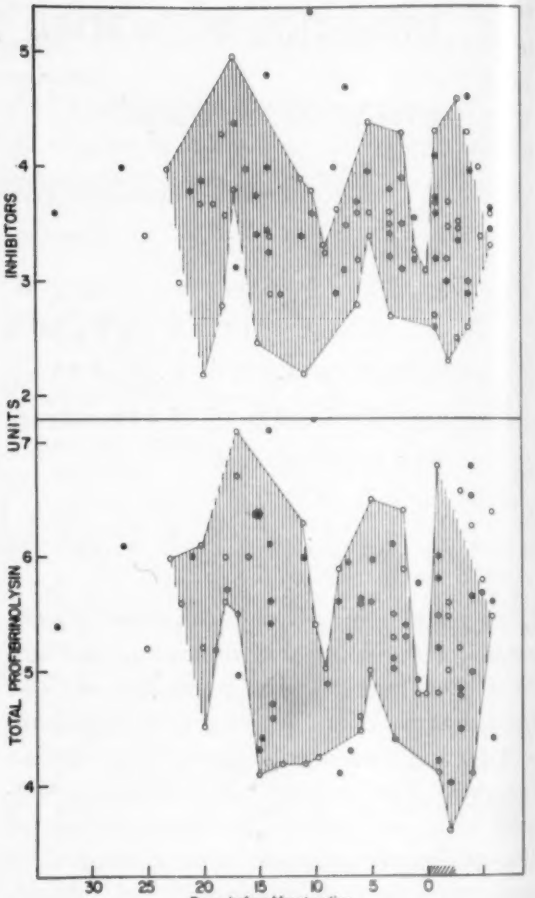


Fig. 2. Composite graph for inhibitor and total profibrinolysin levels in the ovulatory and anovulatory women. ○ ovulatory women's enzyme levels; • anovulatory women's enzyme levels.

Materials and methods

Four groups of individuals were studied:

1. Ten normal women with regular ovulatory cycles of 28 to 32 days, documented by means of basal body temperature charts and endometrial biopsies.

2. Eleven anovulatory women with dysfunctional bleeding selected from the Sloane Endocrine Clinic, in whom previous studies indicated consistent lack of ovulation and in whom endometrial patterns varied from active proliferation to hyperplasia. Organic and systemic causes of uterine bleeding were excluded. Ovarian function was evaluated by means of basal body temperature charts and endometrial biopsies during the study period.

3. Two women subjected to bilateral oophorectomy at the time of hysterectomy for uterine fibromyomas several years previously.

4. Two normal young men.

The following factors were determined at weekly intervals: fibrinogen, determined by the method of Ratnoff and Menzie[25]; free profibrinolysin, determined by the hydrolysis of casein by plasma activated by streptokinase; total profibrinolysin, determined by the hydrolysis of casein by euglobulin precipitated from plasma and activated by streptokinase; and inhibitors, estimated by the difference between free and total profibrinolysin.[8] Each of the above factors was measured 96 times in the ovulatory group and 94 times in the anovulatory group. Four levels were obtained for each of the 2

surgically castrated women. Four determinations were obtained on one male and three on the other.

Results

The mean fibrinogen, total profibrinolysin, and inhibitor levels found in the ovulatory and anovulatory groups are shown in Table I. The mean values for each subject were calculated and these individual means were then averaged for each group. The values for the ovulatory group are based on 96 determinations of each factor; the number of determinations on each of 10 subjects varied from 3 to 17 over a period of one or more cycles. Ninety-four determinations were made in the anovulatory group over a period of 4 to 12 weeks; each of the 11 individuals was studied from 5 to 15 times. The mean fibrinogen level for the ovulatory group was 256 mg. per cent with a standard deviation of ±29.8 and 323 mg. per cent with a standard deviation of ±54.6 for the anovulatory group. The differences between fibrinogen levels in the two groups show statistical significance with a probability of less than 0.01. The groups, however, are too small to ascribe a clinical significance to these differences. The profibrinolysin and inhibitors show essentially identical means for the two groups.

Castrated women and normal young men. All levels remain essentially constant for each subject in these two groups (Table II).

The fibrinogen and fibrinolytic enzyme levels shown in Figs. 1 and 2 are plotted as a composite graph according to the day before the onset of menstrual or anovulatory bleeding. These data consist of 59 determinations in 8 ovulatory women, and 35 determinations in 6 anovulatory women. Ovulatory subjects were included if the cycle length was from 28 to 32 days, if ovulation was documented by endometrial biopsy or basal body temperature charts during the cycle studied, and if menstrual periods were reliably recorded. The anovulatory levels include only those observations made within 35 days before the onset of documented and spontaneous anovulatory bleeding.

Ovulatory women. Adjacent minimum and maximum values for fibrinogen, profibrinolysin, and inhibitors were connected by a line in order to demonstrate the range of monthly alterations in these determinations (Figs. 1 and 2). In these composite graphs, two peaks occurred between episodes of menstruation in ovulatory cycles. The increase in circulating profibrinolysin and inhibitors preceded the rise in fibrinogen and occurred at approximately the time of the ovulatory peak of estrogen excretion. A second elevation in all these factors was observed from 3 to 6 days before the beginning of a menstrual period. All factors declined premenstrually and gradually rose after the onset of menses. Fig. 3 demonstrates the fibrinogen and enzyme fluctuation pattern according to basal body tem-

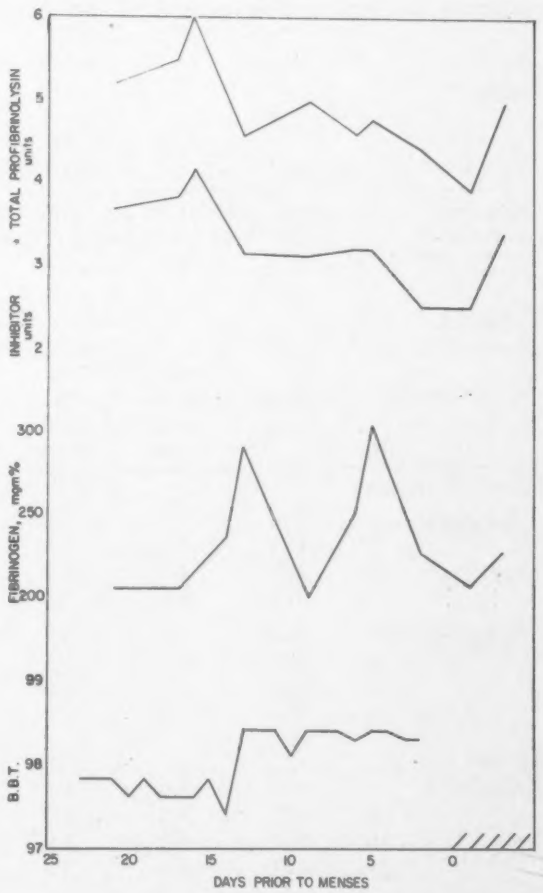


Fig. 3. Total profibrinolysin, inhibitors, and fibrinogen levels superimposed on basal body temperature chart of an ovulatory subject.

perature graph in a single ovulatory subject. In individual subjects, the fluctuating pattern of one month could be superimposed on the same pattern of a subsequent month with minimal variations.

Anovulatory women. The fibrinogen levels in this group range from 250 to 517 mg. per cent as contrasted to a range of 180 to 355 mg. per cent in ovulatory women. An irregular pattern lacking the rhythmical rise and fall in ovulatory cycles is apparent. Total profibrinolysin and inhibitor levels are essentially within the same range for both groups, but the rhythmic alterations were not detected in anovulatory women. However, both factors declined before the onset of bleeding and rose again soon afterwards.

Comment

The daily urinary estrogen excretion during the normal menstrual cycle varies in a constant fashion and it is highest just before the thermal shift. A second lesser peak occurs during the luteal phase. Frank,[26] Taylor,[27] and numerous other investigators have shown this pattern by bioassay methods. Recently Brown, Kellar, and Matthew,[28] by means of more precise biochemical determinations, have confirmed this (Fig. 4) in their publication. The fibrinogen, profibrinolysin, and inhibitors show a strikingly similar pattern with peak blood concentration of these substances being found 1 or 2 days after a described estrogen excretion peak.

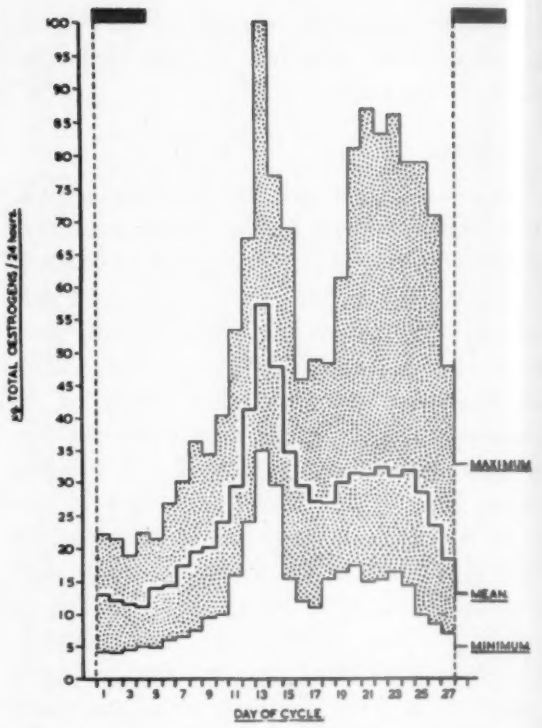


Fig. 4. Mean, maximum, and minimum levels of total urinary daily estrogens excretions in 16 ovulatory women. (From Brown, Kellar, and Matthew.[28])

The total profibrinolysin and the inhibitors apparently reach a peak approximately 17 days before the onset of menstruation and a lesser peak approximately 5 days before bleeding. The first peak in fibrinogen occurs 10 to 11 days before the subsequent period and a less marked elevation 3 to 4 days before. The similarity of the cyclic patterns may reflect the effect of estrogen upon these factors. It may be postulated that an increase in antifibrinolysin may inhibit activa-

Table I

	Fibrinogen	*Total profibrinolysin*	*Inhibitors*
Ovulatory	256 ± 29.8	5.53 ± 0.64	3.50 ± 0.42
Anovulatory	323 ± 54.6	5.64 ± 0.70	3.67 ± 0.33

Table II

	Day	*Fibrinogen (mg. %)*	*Total profibrinolysin (units)*	*Inhibitors (units)*
Castrated women				
Subject 1	1	309	6.4	3.7
	8	313	6.0	3.5
	16	306	6.5	3.9
	24	314	7.6	4.8
Subject 2	1	290	5.3	3.1
	8	276	6.7	4.5
	16	288	6.7	4.8
	24	260	5.4	3.3
Normal men				
Subject 1	1	218	5.0	3.5
	8	222	5.0	3.7
	16	187	5.3	3.9
	24	192	5.4	3.8
Subject 2	1	200	5.6	3.5
	8	195	5.7	3.8
	16	199	5.4	3.4

tion of profibrinolysin and subsequent hydrolysis of fibrinogen, thus permitting these two substances to accumulate.

They[28] have also demonstrated that anovulatory cycles may be associated with constant or fluctuating estrogen excretion and that the degree of endometrial proliferation is correlated with the level of estrogen measured in the urine. Therefore, the higher fibrinogen levels in the group of anovulatory women with highly active endometria may reflect a greater than normal estrogen production, and the widely fluctuating levels (not seen in men and castrated women) might be due to erratic rate of estrogen secretion by the ovary.

Summary

1. There is a cyclic variation in fibrinogen, profibrinolysin, and inhibitors (antifibrinolysin) in normal ovulatory women which seems related to the pattern of urinary estrogen excretion.

2. Anovulatory patients in this series show greater fluctuation of all factors and higher levels of fibrinogen without a cyclic pattern.

3. Males and surgically castrated females show apparently constant levels of all factors.

We wish to thank Mrs. V. Skrodelis for the laboratory assistance.

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Influence of ovarian function on the fibrinolytic enzyme system

II. Influence of exogenous steroids

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VARIATIONS in the fibrinolytic system during normal and anovulatory menstrual cycles were discussed in Part I. Hormonal preparations were administered to some of these same patients in order to determine the influence of exogenous steroids on the system.

Methods and materials

The same laboratory methods and patient material were employed as were described in the preceding report. The subjects included 2 women with normal ovulatory menstrual cycles, and 6 anovulatory patients, 2 with bleeding and 4 with oligomenorrhea. After a thorough study of each patient, involving from 5 to 15 determinations of fibrinogen, profibrinolysin, and inhibitors, at approximately weekly intervals, different steroids were administered orally to the patients for a period of 12 to 17 days. The preparations used were a conjugated estrogen (Premarin), 17 α-ethynyl-17 hydroxy-5(10)-estren-3-one with 1.5 per cent ethynylestradiol 3-methyl ether (Enovid), ethynylestradiol 3-methyl ether (EE3ME), and 19-nor-17 α-ethynyltestosterone (Norlutin). From 1 to 5 determinations were carried out for each patient during hormonal treatment.

The pretreatment levels on each patient were averaged, as were the levels obtained on medication, for the comparison of results of individual patients. In the statistical analysis of the effect of the drugs, the means of individual patients before and after a given medication were averaged and compared with use of the "t" test for paired results.[1]

In addition, intravenous conjugated equine estrogens were administered to 2 patients. One patient was found to have a low fibrinogen level following dilatation and curettage; the other patient had an intrauterine fetal death of 6 weeks' duration. She had been followed at frequent intervals during a period in which the fibrinogen level had decreased from 332 mg. per cent shortly before the death of the fetus to 168 mg. per cent at the time of drug administration. In addition to a study of the fibrinolytic system, thromboplastin generation tests were performed by the method of Biggs and MacFarlane[2] but using barium sulfate–treated plasma as suggested by Duckert and associates.[3]

Results

Fig. 1 shows the average figures for each patient before and after the different drugs.

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With oral administration of 5 mg. of conjugated equine estrogens, results of fibrinogen varied from patient to patient. However, the profibrinolysin showed slight rises in all cases and the antifibrinolysin in all but one. With 10 mg. conjugated equine estrogens, increases in profibrinolysin again occurred in all cases and in 5 of 7 studies of antifibrinolysin. Fibrinogen figures were again varied. Except for one patient with decreases in inhibitor levels, increases were obtained for all factors by the patients on norethynodrel (Enovid). All factors rose in the patients receiving EE3ME. Twenty milligrams per day of norethindrone (Norlutin) produced slight elevations in all factors, while 10 mg. per day of norethindrone acetate was followed by tremendous rises in profibrinolysin and inhibitor levels but a slight decrease in fibrinogen. Active proteolysis was observed in the euglobulin fraction of this patient during the period when she was receiving the drug. Small but significant levels of active proteolysis by the euglobulin fraction (0.2 to 0.8 units) were also frequently found in patients on norethynodrel and EE3ME but this rarely occurred in the control samples or on conjugated equine estrogen.

Table I shows a statistical analysis by the "t" test for paired results obtained by averaging the means for each patient on an individual drug. The fibrinogen levels on conjugated equine estrogens were not significantly different from those obtained before administration of the drug but significantly higher levels ($P < 0.01$) were produced by norethynodrel, and borderline significance by EE3ME ($P < 0.05$).

Increases in profibrinolysin were highly significant ($P < 0.001$) for 5 and 10 mg. conjugated equine estrogens and significant ($P < 0.01$) for norethynodrel and EE3ME. Although the increase in units was greater for the last two drugs, the smaller number of patients makes for a lower statistical significance. The levels of antifibrinolysin showed no significant changes on 5 mg. conjugated equine estrogens, borderline significance ($P < 0.10$) on 10 mg. of it and norethynodrel, and significance on EE3ME ($P < 0.01$).

Fig. 2 Shows the results obtained by giving large doses of intravenous conjugated equine estrogens (20 mg. per hour for 3 hours) to a patient with mild hypofibrinogenemia caused by a longstanding intrauterine fetal death. An initial rise in all factors was obtained and was followed by a decrease in profibrinolysin and inhibitors in the second hour after initiation of treatment and later by a drop in fibrinogen level. The euglobulin lysis time which was greater than 420 minutes in the predrug and one hour samples was 120 minutes at 2 hours, and 45

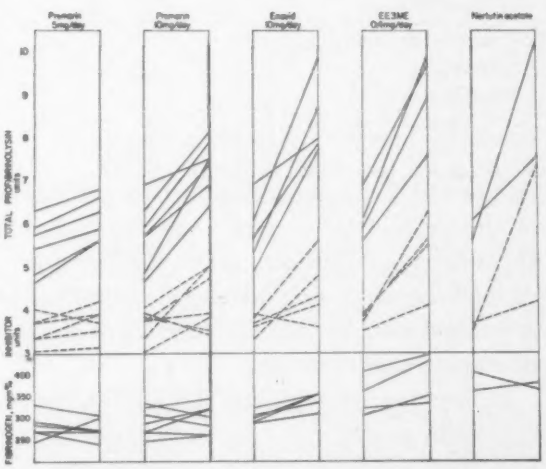


Fig. 1. Average levels of fibrinogen, total profibrinolysin, and inhibitors obtained in individual patients before and after hormonal preparations.

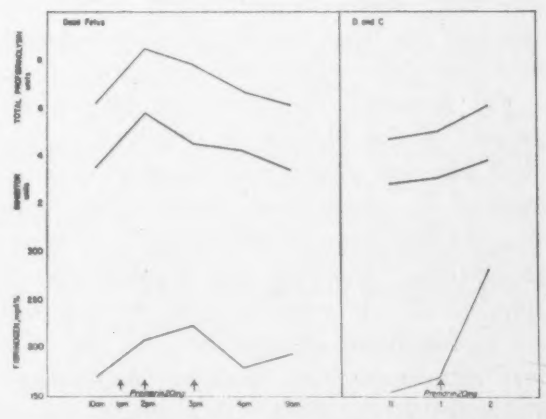


Fig. 2. Changes in the fibrinolytic system following intravenous administration of conjugated equine estrogens in 2 patients with mild hypofibrinogenemia.

Table I. Changes in the fibrinolytic system

Hormonal preparation	*No. of patients*	*Fibrinogen (mg. %)*	*Profibrinolysin (units)*	*Inhibitors (units)*
Control	6	278 ± 32	5.53 ± 0.65	3.55 ± 0.35
5 mg. conjugated equine estrogens		271 ± 30	6.14 ± 0.51	3.71 ± 0.38
Difference		-7	+0.61	+0.35
Probability		0.7	<0.001*	0.17
Control	7	288 ± 33	5.76 ± 0.81	3.63 ± 0.37
10 mg. conjugated equine estrogens		297 ± 33	7.40 ± 0.61	4.19 ± 0.69
Difference		+9	+1.64	+0.56
Probability		0.50	<0.001*	<0.10†
Control	5	299 ± 15	5.84 ± 0.64	3.66 ± 0.22
Norethynodrel		342 ± 23	8.46 ± 0.89	4.48 ± 0.76
Difference		+43	+2.62	+0.82
Probability		<0.01‡	<0.01‡	<0.10†
Control	4	349 ± 46	6.13 ± 0.56	3.73 ± 0.13
EE3ME		391 ± 56	9.05 ± 1.05	5.13 ± 0.92
Difference		+42	2.92	1.85
Probability		<0.05†	<0.01‡	<0.01‡

*Highly significant.

†Borderline.

‡Significant.

minutes at 3 hours, indicating an activation of the fibrinolytic system. Fig. 2 also shows the increases obtained after administration of intravenous conjugated equine estrogens to a patient with hypofibrinogenemia following dilatation and curettage.

In the patient with the dead fetus, thromboplastin generation had been reduced before the estrogens were given (Fig. 3). Three hours after initiation of therapy thromboplastin generation had returned to normal but was again deficient by the following morning. Early in pregnancy, before the death of the fetus, the thromboplastin generation had been within normal limits.

Fig. 4 shows the changes in the various factors of the fibrinolytic system in a patient who was treated with norethynodrel for control of intermittent spotting for more than 14 days from an active proliferative endometrium. Bleeding was stopped after 2 days on 20 mg. norethynodrel per day and no further bleeding occurred until the drug was withdrawn after 20 days. The patient responded to the drug with a distinct rise in profibrinolysin, increase in inhibitors, and a delayed elevation of the fibrinogen level. On drug therapy, some active proteolysis by the euglobulin precipitate was observed for the first time.

Comment

These data indicate that the estrogens and the 19-norsteroid compounds used do exert an influence on the fibrinolytic enzyme system. The results of individual patients, before and after administration of these hormones, and the averages of groups of patients, before and after, showed significant increases in profibrinolysin levels and somewhat less marked elevations in the antifibrinolysin as measured by the methods used here. Fibrinogen levels showed a variable pattern. In addition, active fibrinolysin was observed following intravenous conjugated equine estrogens as well as following prolonged oral administration of norethynodrel, EE3ME, and norethindrone. This usually occurred after the profibrinolysin levels had become abnormally elevated.

The mechanism for these changes cannot be postulated from the work presented here. It may be that the primary effect increases the inhibitor level[4] which would have the effect of slowing down the spontaneous activation of the profibrinolysin, thus permitting

the concentration of the precursor to build up. This would also have the effect of reducing the hydrolysis of fibrinogen and thus causing higher levels of this substance. Continued administration of the drug apparently results in an activation of the profibrinolysin after unusually high levels have accumulated. The active fibrinolysin may then be responsible for hydrolysis of fibrinogen.

The influence of estrogens in increasing fibrinogen, profibrinolysin, and inhibitor levels in patients with carcinoma of the prostate has been reported previously by Phillips and Skrodelis.[5] Tagnon and associates[6] and Prout and associates[7] have observed an increase in fibrinogen and a decrease in active fibrinolysin in this same group of patients on administration of estrogens and the opposite effect on administration of testosterone. The implication of these results has been that the estrogens acted by decreasing the size and activity of the prostatic tumor and thus stopping the flow of prostatic fluid into the blood stream. The results presented here, however, suggest that estrogens may have a more direct effect either by initially inhibiting the activation of the profibrinolysin or by stimulating the production of all factors of the fibrinolytic system. In a mechanism previously postulated, Schersten[4] has stated that estrogens inhibit fibrinolytic activity and that administration is followed by a rise in fibrinogen level of the blood.

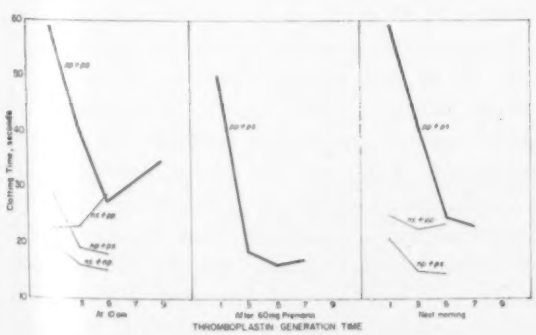


Fig. 3. Thromboplastin generation curves obtained from the blood of a woman with hypofibrinogenemia and intrauterine fetal death before and after intravenous conjugated equine estrogens: *pp*, patient's plasma; *ps*, patient's serum; *np*, normal plasma; *ns*, normal serum.

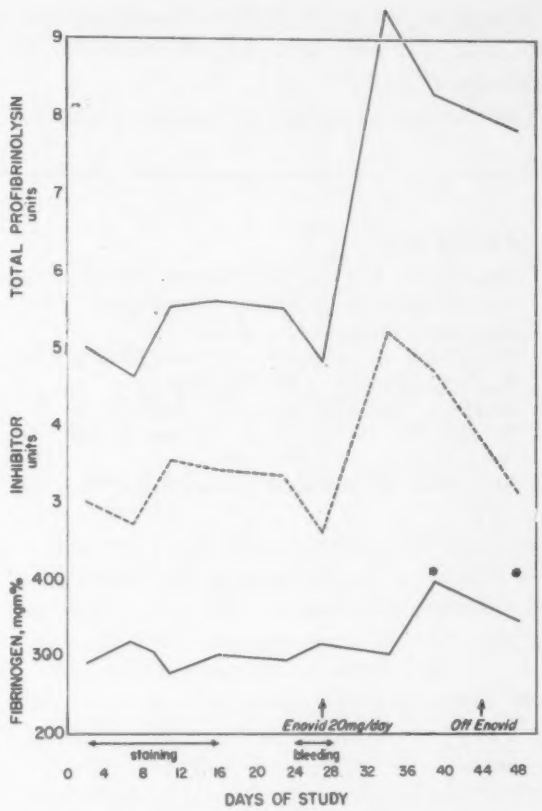


Fig. 4. Changes in the fibrinolytic system in a woman treated for intermittent bleeding with 20 mg. oral norethynodrel per day. The asterisk (*) indicates active proteolysis by euglobulin precipitate.

The results obtained by the use of introvenous conjugated equine estrogens suggest that this substance might be useful in treating cases of hypofibrinogenemia either with or without concomitant fibrinogen therapy. Not only did the fibrinogen and inhibitor levels show initial increases following the drug but thromboplastin generation, which had been decidedly impaired, returned to normal after its administration. This may be connected with a decrease in anticoagulant as suggested by Johnson[8] or it may be a more direct stimulation of production of factors responsible for thromboplastin generation. No anticoagulant studies were performed in this case.

Summary

Oral administration of exogenous estrogen preparations and of norethindrone appear to cause an increase in profibrinolysin and anti-

fibrinolysin. Administration of norethynodrel and EE3ME also causes increases in fibrinogen levels.

Intravenous conjugated equine estrogens produce short-lived elevations of fibrinogen levels and other factors and may be useful in treating borderline cases of hypofibrinogenemia.

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New adjunctive therapy in purpura in the female

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MUCH has been written in recent years about the etiology and treatment of idiopathic thrombocytopenic purpura. As in all of medicine, certain routine practices must be followed but the patient must have individualized therapy for the best final outcome. Results of therapy in this disease are in general unpredictable although the chief modes are now accepted as being corticosteroids, platelet transfusions, and splenectomy. We are presenting this case report as one in which not only were all forms of treatment necessary to control bleeding, but also in which a previously unreported adjunctive therapy was employed to control the initial complaint of menorrhagia.

Case report

Miss B. L., a 17-year-old single nulligravida, was admitted to the Highland Park Hospital with the chief complaint of profuse and prolonged vaginal bleeding of about 25 days' duration, accompanied by weakness and dizziness.

Menarche occurred at the age of 15 with irregular menses for the first year but regular menses for the past year every 28 days lasting 6 days with moderate flow. Her last normal period was February 5, 1959. Since March 8, 1959, she had been bleeding intermittently profusely and lightly. Physical examination revealed extreme pallor with a few petechiae on the legs. The uterus was erect, small, and firm. The adnexa were normal. The cervix was patulous and slightly softened. There was moderate bleeding from the cervical os. The pulse rate was 146 and blood pressure was 90/60. There was a hemic cardiac murmur. The hemoglobin level was 5.0 Gm. per 100 ml., and platelets were called "normal."

She was given 20 mg. of conjugated estrogens (Premarin) intravenously and 5 blood transfusions, but bleeding remained profuse for the next 12 hours. Intravenous estrogen was repeated but no hemostatic effect was obtained. Curettage was performed about 20 hours after admission with almost immediate cessation of bleeding. The pathologic report was physiologic hyperplasia of the endometrium, proliferative phase.

On the next day, April 6, 1959, she began to show more petechiae over her arms and body, and there were some small purpuric areas; she had one episode of epistaxis. At this time, the platelet count which had been called normal previously was found to be 14,000 and the bleeding time was over 20 minutes. From this time on, she bled from every body orifice except the vagina. She had epistaxis, bleeding from the gums, gastrointestinal bleeding, hematuria, and multiple purpuric spots over her body. She received therapy with corticosteroids, nitrogen mustard, massive doses of ascorbic acid, repeated transfusions, large doses of citrus bioflavonoids, vitamins A and D, all to no avail. On April 13, 1959, splenectomy with removal of several small accessory spleens, was performed; about 2,000 c.c. of liquid blood was found in the peritoneal cavity. She also required nasal packing to control epistaxis. Her postoperative course was stormy, with continued oozing from the peritoneal cavity through drains and the splenectomy incision. She received continued medical treatment as above plus antibiotics, platelet and whole blood transfusions; a total of 12,500 c.c. of whole blood was given. Urinary output continued normally throughout

and hematuria ceased 2 days postoperatively. On April 20, 1959, she began to show signs of improvement and abdominal drainage of blood slowed down. 6-Mercaptopurine was given for 1 week to suppress platelet antibodies. The liver was found to be enlarged on May 7, 1959, and x-ray therapy (100 r for 3 doses) was given to the liver area.

She improved quite rapidly from then on and was discharged on May 17, 1959, to be followed on steroids and iron therapy after she left the hospital. At the time of discharge, the platelet count was 192,000, hemoglobin level, 12.2 Gm. per 100 ml., and the hematocrit determination was 40 per cent.

On June 22, 1959, she was again admitted with profuse vaginal bleeding. Her general condition had been good, but on June 13, 1959, she began to menstruate and continued flowing profusely until admission, at which time the hemoglobin level was 8.8 Gm. per 100 ml. and the platelets were down to 56,000. On admission, the only positive findings were a slightly enlarged liver and numerous petechiae over the lower extremities. Pelvic examination was negative. In view of the rapid response previously, a curettage was performed and an intrauterine pack inserted. The pathologic report was the same as formerly—physiologic hyperplasia of the endometrium, proliferative phase. She received 1,000 c.c. whole blood and was discharged on June 26, 1959, to continue on steroids. She was also started on weekly injections of estradiol valerate (Delestrogen) 5 mg., and hydroxyprogesterone caproate (Delalutin) 250 mg., in an attempt to prevent menses for a period of about 6 months to allow her to obtain the maximum benefits of the splenectomy and prevent further menstrual blood loss. During this hospitalization, a patchy retinal atrophy on the right and a partial left optic nerve atrophy were found; these were also due to purpuric bleeding. They improved gradually over a period of weeks.

She was admitted again on July 19, 1959, because of profound anemia; she had had some intermittent bleeding per vaginam because of breakthrough bleeding in the attempt to adjust the dosage of estrogen-progesterone injections. She received 1,500 c.c. of whole blood and the bleeding subsided. She continued under the care of her family physician for the next 5 months and received weekly injections of the same estrogen-progesterone products until Dec. 1, 1959. She had occasional spotting but no menstrual flow until December 7. She then had a normal 4 day menstrual period. On December 19, examination revealed a normal-sized uterus in 3 degrees retroflexion with a smooth conical cervix; the adnexa were palpable and normal. March 12, 1960, she was examined and again found to have a normal pelvic status. Menses had been regular every 26 to 28 days lasting 4 to 5 days and in completely normal amounts.

Comment

In the adult female, the initial manifestation of idiopathic thrombocytopenic purpura is frequently menometrorrhagia. In a recent series of 26 adults of whom 21 were female,[1] 6 patients (almost 30 per cent of the females) showed menorrhagia as a major complaint. Although ITP is not common, most gynecologic textbooks mention it in the differential diagnosis of menorrhagia. In a report of 15 cases of purpura first manifesting as menorrhagia, Reich and associates[2] stated that a rule had been endorsed at their gynecology clinics which urged a screening platelet count and if necessary a thorough hematologic investigation for all patients exhibiting a hemorrhagic tendency.

Firat and Stutzman[3] recently reported that intravenous estrogens are of no apparent value for control of thrombocytopenic bleeding. They found no significant change in the thrombocyte counts on administration of the usual dose. In our case, the vaginal bleeding did not respond to estrogens or transfusions; however the bleeding stopped promptly after curettage on 2 occasions. We are unable to explain this but feel that curettage should be performed for its apparent hemostatic effect and to rule out gross pathologic conditions if the bleeding is not controlled medically.

It has been stated that the patient with "acute" ITP should have a 100 per cent chance to achieve full recovery after splenectomy[4]; however, the full beneficial effects may not be evident until several months after splenectomy. Since our patient had a relapse in association with the first

menses 2 months after splenectomy, it was decided that an attempt should be made to obviate this source of bleeding for several months. She had another relapse 1 month later due to breakthrough bleeding occurring as a result of attempted adjustment of the estrogen-progesterone dosage. From that time on however, she was kept from menstruating for 5 months and she also exhibited no other hemorrhagic tendencies. When the estrogen-progesterone injections were stopped, she experienced a normal menstrual period and to date has continued to have a normal menstrual pattern. We feel that a physiologic hormonal regimen of menstrual suppression should be utilized in all women with ITP treated by splenectomy for at least 6 months postoperatively. It is theoretically possible that this regimen might also be used in those acute cases which respond to steroids alone, especially in view of recent work which shows that corticosteroids may be effective alone if given in massive doses.[5]

Summary

A case of idiopathic thrombocytopenic purpura has been reported in a patient who presented the initial complaint of menorrhagia. Whereas the usual treatment of steroids, platelet transfusions, and splenectomy were finally effective in controlling the hemorrhages, a suggestion has been presented for the temporary suppression of menstruation by physiologic hormonal means to control a major source of blood loss in the female.

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Effect of progesterone on experimental endometrial hyperplasia

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IN SPITE of the fact that endometrial hyperplasia is a common problem in medical practice, its treatment is far from correct. Too often the physician is content with the disappearance of bleeding without obtaining further information about the state of the endometrium.

In order to study the effects of some hormones upon endometrial hyperplasia, we undertook a series of experiments. In previous work done in this laboratory[1] it was found that daily doses of 10 and 20 mg. of testosterone propionate did not induce regression of endometrial hyperplasia in female rabbits as long as the stimulating agent, beta-estradiol, continued to be administered.

This report deals, first, with the influence of progesterone upon endometrial hyperplasia induced by estrogen administration and, second, with the preventive action of progesterone upon the development of such hyperplasia.

Material and methods

For both experiments a total of 52 female rabbits were used. They weighed from 2,200 to 2,800 grams and were not spayed. The experiments were done in several cycles. A biopsy specimen was taken from each rabbit at the end of each cycle.

Various concentrations of the drugs, dissolved in a mixture of ether and oil as indicated in the text, were administered intramuscularly in various doses.

From the Department of Pathology, Medical School of the Universidad Michoacana de San Nicolás de Hidalgo.

The uterine biopsy specimens were fixed in formalin and cold 80 per cent alcohol and stained with: (1) hematoxylin and eosin; (2) periodic acid–Schiff (PAS) with and without digestion with saliva; and (3) alkaline phosphatase (Gomori).

The animals were fed Purina Rabbit Chow and fresh clover ad libitum.

Results and comment

Experiment I. Treatment of endometrial hyperplasia.

First cycle. Groups of 2 to 4 rabbit does were separated from males and kept in cages for a period of 4 to 6 months. A biopsy specimen was taken before the start of hormone administration. This specimen served as a control for each animal, since individual variations in the endometrial pattern are frequently observed.

Second cycle. Beta-estradiol, 1 mg. daily, was injected for 30 to 40 days. Biopsy specimens taken at the end of this cycle showed endometrial hyperplasia in every rabbit. This was manifested by increase in thickness of the endometrium, increase in the number of glands, gland cyst formation, and thickening of endometrial folds. The superficial and glandular epithelium showed increase in thickness varying from simple cuboidal in the control biopsy to cylindrical pseudostratified in the treated animal.

The influence of beta-estradiol was manifested also by the presence of PAS-positive material which was not digested by saliva. This secretion appeared mainly in the cytoplasm of the superficial epithelium and was

less abundant in the cytoplasm of the glandular epithelium. The same type of secretion was found, but in lesser amounts, covering the endometrial surface and within the lumen of the glands. This secretion has been reported in women under physiologic and pathologic conditions.[2, 3] The estrogenic influence was manifested in the endometrial stroma by capillary proliferation, varying in degree from one rabbit to another, and in the muscle fibers, which showed increase in thickness.

Third cycle. The third cycle was dedicated to treatment of previously induced hyperplasia. For this purpose the animals were injected with a mixture of progesterone and beta-estradiol, the object being to maintain stimulation of the endometrium with the beta-estradiol during administration of progesterone.

During this cycle the animals were divided into Groups A, B, and C. Groups A and B received daily injections, for 40 days, of 20 and 30 mg. of progesterone, respectively, mixed with 1 mg. of beta-estradiol. In Group C, the control group, all treatment was stopped.

All 7 rabbits of Group A (progesterone 20 mg., beta-estradiol 1 mg.) showed increase of endometrial hyperplasia. The positive PAS secretion and alkaline phosphatase activity were also increased. There were no histologic signs of regression of endometrial hyperplasia (Table I).

All 9 rabbits of Group B (progesterone 30 mg., beta-estradiol 1 mg.) also showed increase in the histologic signs of endometrial hyperplasia, increase of positive PAS secretion, and increase of alkaline phosphatase activity.

All 4 animals of Group C (suspension of treatment) showed regression of the endometrial hyperplasia. Nevertheless, the positive PAS secretion was slightly increased. Activity of the alkaline phosphatase remained about the same as in the previous cycle.

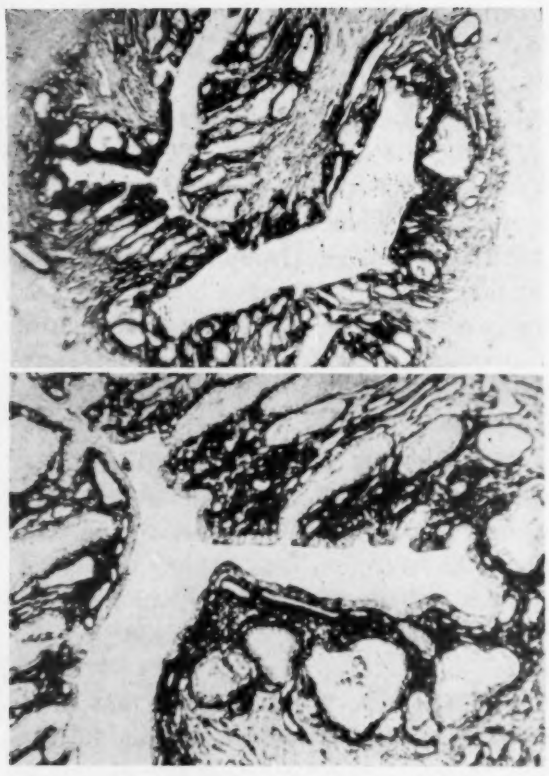
This first experiment indicates that endometrial hyperplasia regresses within 40 days of suspending administration of estrogen. If estrogen is continued, progesterone in 20 and 30 mg. daily doses does not induce regressive changes of the hyperplastic endometrium in the rabbit (Figs. 1 and 2).

Table I. Treatment of endometrial hyperplasia with mixtures of progesterone and beta-estradiol for 40 days

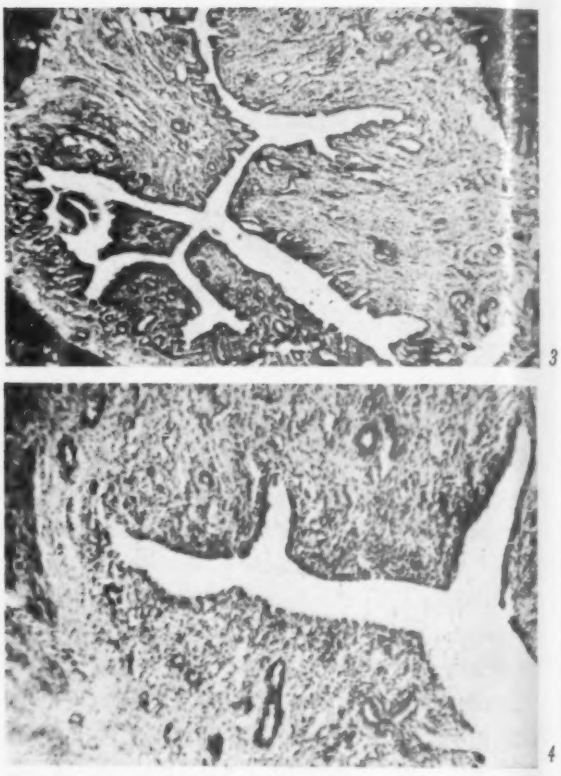
Group	*Dose*	*No. of rabbits*	*Endometrial hyperplasia*	*PAS*	*Alkaline phosphatase*
A	Progesterone, 20 mg. β-estradiol, 1 mg.	7	Increase in 7	Increase	Increase
B	Progesterone, 30 mg. β-estradiol, 1 mg.	9	Increase in 9	Increase	Increase
C	No treatment	4	Regression in 4	Slight increase	Remained about the same

Table II. Prevention of endometrial hyperplasia with progesterone

Group	*Dose*	*No. of rabbits*	*Endometrial hyperplasia*	*PAS*	*Alkaline phosphatase*
A	Progesterone, 10 mg. β-estradiol, 1 mg.	8	Present in 8	Increase	Slight increase
B	Progesterone, 25 mg. β-estradiol, 1 mg.	9	Slight in 2	Negative or slight	Unchanged
C	Progesterone, 35 mg. β-estradiol, 1 mg.	6	Absent in all 6	Negative or slight	Unchanged
D	Progesterone, 50 mg. β-estradiol, 1 mg.	9	Endometrial regression	Negative or slight	Unchanged



Figs. 1 and 2. Endometrial hyperplasia in rabbits developed under the influence of beta-estradiol. These were treated posteriorly with daily injection of progesterone, 30 mg., and beta estradiol, 1 mg. The hyperplastic changes remained unchanged.



Figs. 3 and 4. Rabbits treated daily with progesterone, 50 mg., and beta-estradiol, 1 mg. After 40 days of treatment there was endometrial regression instead of endometrial hyperplasia.

Experiment II. Prevention of endometrial hyperplasia. Experiment II was divided into two cycles; 32 rabbits were used.

First cycle. The does were separated from males and confined in cages for 4 to 6 months.

Second cycle. The rabbits were divided into four groups, A, B, C, and D. Each group received 40 daily injections of 1 mg. of beta-estradiol plus variable amounts of progesterone as follows: 10 mg. for Group A; 25 mg. for Group B; 35 mg. for Group C; and 50 mg. for Group D.

In Group A (8 rabbits; progesterone 10 mg., beta-estradiol 1 mg.) there was well-developed endometrial hyperplasia with all the characteristics mentioned above; 10 mg. of progesterone was not enough to prevent the hyperplastic effect of the estrogen (Table II).

In Group B (9 rabbits; progesterone 25 mg., beta-estradiol 1 mg.) 2 rabbits developed moderate hyperplasia; 7 had no hyperplastic changes; 25 mg. of progesterone afforded considerable protection against beta-estradiol. Some influence of beta-estradiol was manifested, even in those animals without hyperplasia, by the presence of a slight amount of PAS-positive secretion, although the increase of this material was rather irregular, some animals showing it, others not. Alkaline phosphatase activity was not appreciably changed.

In Group C (6 rabbits, progesterone 35 mg., beta-estradiol 1 mg.) all rabbits showed definite protection against the influence of beta-estradiol. None of the animals developed hyperplasia. Alkaline phosphatase and PAS-positive secretion were as in Group B.

The rabbits in Group D (9 rabbits, progesterone 50 mg., beta-estradiol 1 mg.)

not only evidenced lack of hyperplasia, but their endometrium showed marked regressive changes when compared to the control biopsy specimens.

These experiments show that the antiestrogenic properties of progesterone are more successful in preventing endometrial hyperplasia than in treating it. Doses of 25 to 35 mg. of progesterone effectively prevented hyperplasia, while doses of 20 and 30 mg. did not affect the hyperplasia once it was established (Figs. 3 and 4).

Kistner's[4] results in humans are stimulating when compared to our own. He found in 4 women that some progestins may cause cystic and adenomatous hyperplasia to regress.

Summary and conclusions

Daily administration of a mixture of progesterone and beta-estradiol in proportions of 20:1 mg. and 30:1 mg. during 40 days did not produce regression of previously induced endometrial hyperplasia in rabbit does.

Progesterone with beta-estradiol in a proportion of 10:1 mg. administered daily for 40 days did not prevent development of endometrial hyperplasia in normal rabbit does.

Daily injection of progesterone and beta-estradiol in a proportion of 25:1 mg. afforded definite protection against the hyperplastic effects of estrogen to 7 out of 9 animals; the same mixture in a proportion of 35:1 mg. gave complete protection.

When a mixture of progesterone plus 1 mg. of beta-estradiol was injected, the endometrium not only failed to undergo hyperplasia but presented marked regressive changes.

Laboratorios Syntex of Mexico City kindly furnished the hormones for this work.

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Clinical usage of a saturated aqueous solution of diethylstilbestrol

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THE intravaginal application of estrogen is employed in the treatment of local vaginal conditions, in which it serves to increase the cornification of the vaginal epithelium in the presence of vaginitis both in prepubertal girls and postmenopausal women. Although it is well known that estrogen is absorbed through the vaginal epithelium, this usage is generally intended to produce local effects primarily, with limitation of systemic activity which is not desired or is contraindicated. Two well-known and widely used proprietary estrogen creams are available. One contains 0.1 mg. dienestrol per gram. The other contains 0.625 mg. conjugated estrogenic substances, principally sodium estrone sulfate, per gram. Diethylstilbestrol vaginal suppositories are also available, containing 0.1 mg. and 0.5 mg. of the drug. The doses of these products, as recommended by the manufacturers, provide, by daily vaginal application, the same amounts of the several estrogens that are customarily prescribed for oral use to provide systemic estrogenic effect. These doses are much higher than necessary for intravaginal use, since the vaginal epithelium responds to about one tenth of the systemic dose when applied locally.[4] The purpose of the present study was to determine if an aqueous solution of estrogen can provide an easily prepared and inexpensive mixture, simple of application, and with controlled and reasonably accurate dosage. A fairly extensive search of the literature failed to reveal any reports of the use of aqueous solutions of estrogen for vaginal or any other local treatment of human patients.

Procedure

The natural estrogenic substances and their derivatives were excluded from this study because of their insolubility in water. Of the 3 synthetic estrogens considered, diethylstilbestrol, dienestrol, and hexestrol, it seems that diethylstilbestrol is the most potent[3] and the most soluble[3] in water. In the several references consulted, the aqueous solubility of diethylstilbestrol is stated to be: "sparingly soluble,"[6] "insoluble,"[2] "almost insoluble,"[7] and "practically insoluble."[5] Dodds[1] had observed that a saturated aqueous solution of diethylstilbestrol contains about 5 mg. of the active substance per liter. Saturated solutions were prepared simply by placing an excess of diethylstilbestrol in distilled water, allowing it to stand at room temperature for at least 48 hours and shaking it occasionally, and filtering.

Five postmenopausal women, aged from 52 to 60 years, who had not menstruated from 3 to 13 years and who were not using estrogens by other means, served as subjects for the original study and subsequently 7 others were added. Each subject was supplied with a saturated aqueous solution of diethylstilbestrol and a urethral glass syringe, one-fourth ounce capacity with an attached rubber bulb. The syringe was one-half inch in diameter and 4 inches in length. To avoid contaminating the solution, they were instructed to pour the proper dose into one of 3 common kitchen measuring spoons, aspirate it into the syringe, inject it high in the vagina while lying supine, and to remain in

this position for 10 to 15 minutes. The measuring spoons were one-fourth, one-half and one teaspoonful in capacity, holding approximately 1, 2, and 4 ml., representing doses of about 0.005 mg., 0.01 mg., and 0.02 mg. of diethylstilbestrol, respectively. No attempt was made to establish the minimal effective dose for each subject. Usually 1 dose daily was employed, but for a few patients, 2 or 3 doses daily were used. The medicine was used in courses of 2 to 6 weeks in length and was discontinued for similar periods. The 5 original subjects repeated the courses four to five times, the others, one or two times.

The degree of cornification was graded on a scale of 1 to 8, the larger number indicating the greatest degree of cornification. This was done both by a study of hanging-drop preparations of the vaginal fluid and of smears on slides stained by the Papanicolaou technique. The effect was also quite apparent upon direct inspection of the vaginal epithelium.

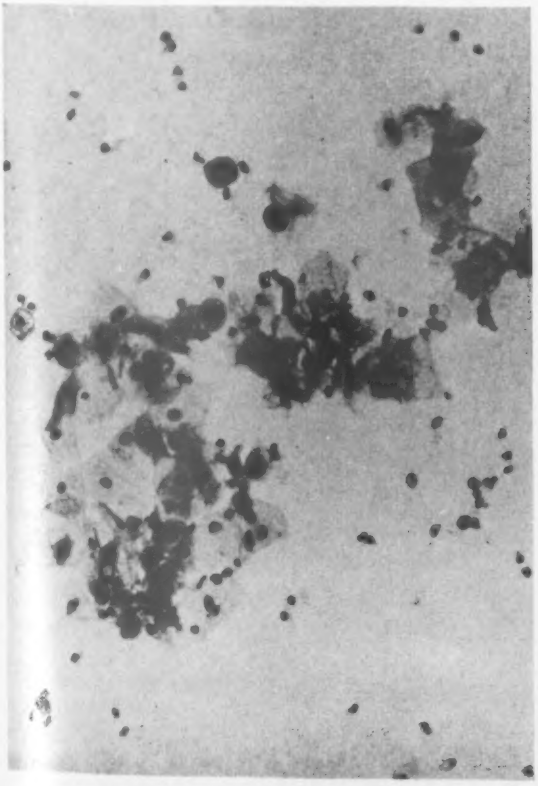


Fig. 1. Before beginning the use of saturated aqueous solution of diethylstilbestrol. Cornification Grade 3. (Papanicolaou stain. ×220; reduced ¼.)

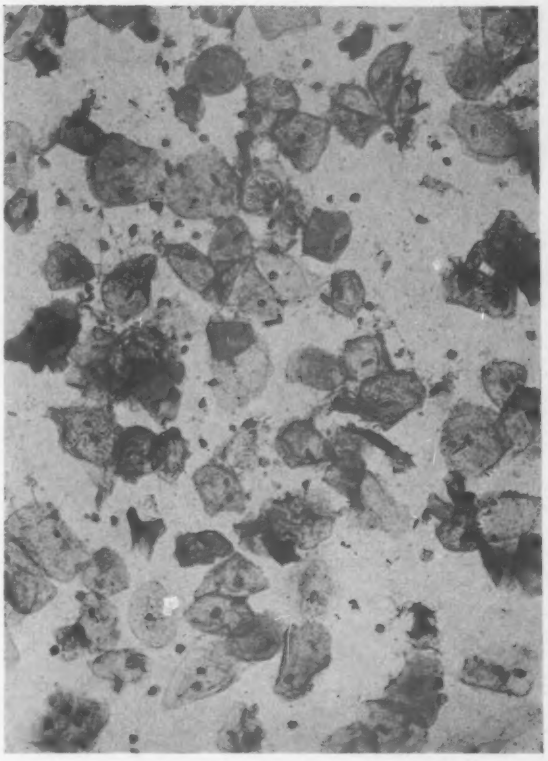


Fig. 2. After daily injection intravaginally for 22 days of 2 ml. saturated aqueous solution of diethylstilbestrol. Cornification Grade 7. (Papanicolaou stain. ×220; reduced ¼.)

It is well known that the use of douches containing plain water or water with nonestrogenic medicaments does not produce estrogenic effect in postmenopausal women. Nevertheless, 2 of the patients were asked to repeat the course using distilled water alone.

Results

All patients showed the response of increased cornification of the vaginal epithelium following the application of the saturated aqueous solution of diethylstilbestrol. Before treatment, the grade of cornification varied from 1 to 3 and, following therapy, it increased to from 6 to 8 (Figs. 1 and 2). The subjective and objective evidence of senile vaginitis promptly disappeared in the patients with this lesion. Two of the patients were wearing supporting pessaries, and the use of the solution relieved the accompanying

vaginitis. Two others had inconclusive vaginal cytology smears and the solution was used for 2 weeks before the tests were repeated. Cornification occurred in both cases, one report became a Negative I while the other became a Positive IV, which subsequently was shown, by biopsy, to be the result of a carcinoma of the cervix. One of the original subjects had been frequently treated for *Trichomonas vaginalis* vaginitis by several methods and had no exacerbations of symptoms while using the solution. No estrogenic effects were noted in the controls.

Summary

The daily instillation of 2.0 to 4.0 ml. of a saturated aqueous solution of diethylstilbestrol is an effective method of producing cornification in the atrophic vagina of the postmenopausal woman. It is a simple, clean, and inexpensive procedure for treating senile vaginitis and, since only minimal total dosages of estrogen are required, it eliminates the risk of inducing undesirable systemic effects.

I wish to thank T. C. Smolen, Ph.G., for providing me with the solutions, Harold M. Lyons, M.D., for grading of the stained slides, C. F. Fluhmann, M.D., for his aid in preparation of the manuscript.

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Iatrogenic stress incontinence of urine

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DESPITE various methods of investigation which are available, the condition of many patients who have urinary stress incontinence presents somewhat of an enigma, not only in respect to causation, but also in the matter of the proper method of treatment of the incontinence. Fortunately, as a result of the efforts of Lapides and many others, we now appreciate the importance of the factors of the length and caliber of the urethra and the tone of the musculature of that structure in the normal maintenance of urinary continence.

Unfortunately, accurate preoperative and postoperative clinical mensuration of the lumen and length of the urethra remains impossible. Similarly, and probably of more importance, there is no method by which the functional capacity of the smooth muscle of the bladder neck and urethra can be appraised qualitatively or quantitatively. Nevertheless, it is generally accepted that to be successful an operative procedure undertaken for stress incontinence should bring about urethral elevation, elongation, and, to a certain extent, diminution of caliber. In practice, the extent of anatomic correction required and the techniques selected to accomplish this objective are based on the rather empiric decision of the individual surgeon, a decision governed largely by his operative experience with the problem or urinary incontinence.

The ordinary patient presenting with mild to moderate incontinence, perhaps associated with a moderate degree of uterovaginal prolapse, can be cured by perineal exercises, by a relatively simple Kelly or Kennedy type of operative procedure, or, it would appear, by almost any of the dozens of operative techniques reported in the literature which involve reconstruction of the urethrovesical area. However, it has been observed repeatedly that the longer the period of postoperative follow-up allowed, the lower will be the rate of cure. Many of the patients treated by the relatively simple measures mentioned above eventually will have (2 to 20-years later) recurrent (secondary) incontinence. As a rule, patients thus afflicted will require more extensive surgical treatment for permanent correction of the urinary incontinence.

Induced or iatrogenic stress incontinence of urine

The foregoing also may apply to another category of incontinent patients—one infrequently described in the literature but a common subject of conversation wherever gynecologists meet—those who have induced or iatrogenic stress incontinence of urine. Depending somewhat upon the iatrogenic agent and the degree of destruction of the neck of the bladder and urethral musculature, patients in this group present the most difficult problems in incontinence encountered in gynecology. The following brief reports may be considered typical of this group.

From the Section of Surgery and the Section of Obstetrics and Gynecology, Mayo Clinic and Mayo Foundation.

The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

Presented at a meeting of the Minnesota Obstetrical and Gynecological Society, Minneapolis, Minnesota, Nov. 19, 1960.

Report of cases

Case 1. This patient, a woman 43 years old who had been pregnant once and delivered successfully, had had enuresis as a child. This condition had persisted until she was of college age. Delivery of a 9 pound, 2 ounce baby had been precipitous. Total abdominal hysterectomy had been performed in 1952 because of uterine fibroids and menorrhagia. Soon thereafter she had first noted a sensation of fullness of the bladder and hesitancy in voiding associated with very minimal stress incontinence. During subsequent years she had continued to notice some degree of urinary hesitancy and occasional urgency and dysuria associated with considerable urinary odor. However, urinary incontinence in the face of stress situations had not been much of a problem. On Dec. 19, 1958, a cystocele had been repaired. This operation had been followed initially by retention of urine. After urologic manipulation and "cauterization" total urinary incontinence developed. The patient had found it necessary to wear a catheter for several months and to discontinue her occupation (schoolteacher) prior to her first visit to the Mayo Clinic in March, 1959.

Examination disclosed a moderate recurrent cystocele. There was much shortening of the anterior vaginal wall and urethra, although the latter appeared to be adequately supported. The entire urethra was patulous and a finger could be inserted into the bladder without occasional distress. Cystoscopic examination showed the urethra to be very short, approximately 1.5 cm. long. The vesicle neck and proximal portion of urethra were very relaxed and there was some deformity of the contour as a result of scarring. The caliber of the urethra was at least 40 Fr., and the general appearance was that seen after resection of the neck of the bladder. The capacity of the bladder was normal, but the expulsive force appeared to be somewhat attenuated, and there were multiple small diverticula of the bladder. However, cystometric studies and neurological examination disclosed nothing of significance. Cystograms revealed considerable irregularity of the outline of the bladder, with the suggestion of multiple small diverticula.

Combined abdominovaginal operation was performed on March 6, 1959. This consisted of a preliminary Kennedy type of repair of the cystocele and plication of the neck of the bladder with constriction of the entire urethra from below, followed by suprapubic urethrovesical suspension. Nonabsorbable sutures placed lateral to the urethra were used, supplemented by additional plicating catgut sutures at the level of the neck of the bladder. The postoperative course was complicated by retention of urine and then by an elevated quantity of residual urine. After 3 weeks' hospitalization, the patient was taught how to catheterize herself and was dismissed to her home. Chemotherapy with sulfisoxazole was prescribed to be taken every fourth week. One year after the operation the patient was continuing to catheterize herself once daily, and residual urine had diminished to about 50 to 100 c.c. She remained entirely continent in respect to urine, was able to return to her teaching and appeared to be well satisfied with the result obtained.

A recent examination shows the patient now voids completely and has no urinary incontinence 2⅓ years postoperatively.

Case 2. A woman 64 years old who had been pregnant eight times and delivered successfully eight times gave a history that was essentially irrelevant except for radium-induced menopause in 1942 for menorrhagia. In July, 1957, she had undergone repair of a cystocele and a rectocele for symptoms suggestive of urgency incontinence, slight stress incontinence, and a sensation of pressure in the bladder. Prolonged retention of urine developed postoperatively, and approximately 2 weeks after the operation a urologist had been called in consultation. Cystoscopic examination at that time disclosed "follicular degeneration of bladder neck with large enfolds present." After a delay of an additional few days, resection of a portion of the edematous neck of the bladder was performed. Urinary incontinence again developed promptly and subsequently a small vesicovaginal fistula was found; however, most of the urine had been observed to leak through the external urethral meatus. In November, 1957, the vesicovaginal fistula had been repaired and another plication of the neck of the bladder had been performed per vaginam. This measure had not resulted in any abatement in the degree of incontinence.

When this patient was referred to us in May, 1958, she was almost totally incontinent. Examination disclosed a shortened anterior vaginal wall with adequate support. However, the urethra appeared to be very short and the external urethral meatus was gaping. Marked incontinence was demonstrable at the time of stress, but it could be corrected by elevation of

the urethrovesical area. Cystoscopic examination disclosed no evidence of fistula. The urethra was dilated proximally and was extremely short, not more than 1 cm. in length. The capacity of the bladder was normal. Results of routine urinalysis and Gram's staining were negative.

Operation was performed May 16, 1958. It consisted of suprapubic urethrovesical suspension with the use of interrupted nonabsorbable sutures lateral to the urethra, supplemented by the use of catgut sutures which elevated and in addition plicated the neck of the bladder. The urethra appeared to be adequately elevated and elongated and somewhat constricted. At the time of dismissal on the sixteenth postoperative day the urethra appeared to be satisfactorily supported and the patient was completely continent in respect to urine, although she did have occasional urgency and some degree of nocturia. Response to a follow-up letter 3 months later disclosed that an excellent result had been obtained.

Case 3. A woman 53 years old, pregnant once and successfully delivered, had undergone treatment of carcinoma of the cervix by radium and x-ray treatment in 1949. This had been followed by the development of radiation proctitis, which gradually subsided with treatment. For several years thereafter she had had episodes of cystitis treated successfully by medical means. Stress incontinence of urine never had been a problem. Nine months prior to her first consultation at the Mayo Clinic in July, 1958, a urologist had noted "ulceration of the bladder neck" at the time of cystoscopic examination. Electric fulguration of the ulcers had been performed. This had been followed promptly by the appearance of almost total urinary stress incontinence.

Pelvic examination disclosed a satisfactory anterior vaginal wall and urethral support. There was considerable postradiation scarring, fixation, and stenosis of the upper part of the vagina. There was obvious urinary incontinence with coughing and straining. Cystoscopically, except for some scarring in the proximal part of the urethra, the bladder and urethra were seen to be essentially normal. Routine urinalysis and Gram's staining showed nothing abnormal.

Urethrovesical suspension was performed on July 24, 1958, in the usual manner, with the use of nonabsorbable silk sutures supplemented by additional sutures of chromic catgut at the level of the neck of the bladder. At the time of surgical dismissal on Aug. 1, 1958, the patient was completely continent in respect to urine, and a follow-up letter later revealed that this result had persisted.

Case 4. A woman 61 years old, pregnant three times and delivered successfully three times, gave a history which included vaginal hysterectomy and repair of a cystocele in 1950 for vaginal relaxation and Grade 1 stress incontinence of urine. The incontinence had been abated considerably for a time, but recurred and increased in severity until a second vaginal repair of a cystocele was performed in 1956, with success. In 1957 considerable dysuria, frequency, and urgency had developed. Irritation of the neck of the bladder and urethra had been noted at cystoscopic examination, and the inflamed area was fulgurated. This had produced complete recurrence of the urinary stress incontinence, which had worsened to Grade 4 (total incontinence) when we were first consulted in July, 1958.

Pelvic examination showed only a short, scarred anterior vaginal wall with minimal cystourethrocele and a short, dilated urethra. Cystoscopic examination confirmed the latter, the urethra being dilated proximally and not more than 1.5 cm. in length. It appeared that the urethra was inadequate because of its short length and dilated caliber. Results of routine urinalysis and other laboratory tests were within normal limits.

Operation was performed on July 17, 1958, and consisted of the standard suprapubic urethrovesical suspension plus plication of the neck of the bladder on its superior surface. Recent consultation (2 years postoperatively) disclosed that the urinary incontinence had been corrected completely. Mild suprapubic aching discomfort suggested (and roentgenologic examination confirmed) the presence of a minor degree of osteitis pubis.

Case 5. A woman 32 years old who had been pregnant once and had been successfully delivered of the infant gave a history which included prolonged labor in 1950. Delivery of the living 9 pound child had been accomplished only by means of a symphysiotomy. The patient had had prolonged retention of urine after delivery, requiring many urologic "treatments." Thereafter she had had marked urinary stress incontinence. Vaginal repair of the neck of the bladder had been accomplished several months after the delivery, but had not brought about

improvement. In 1951 a suprapubic operation of unknown type had been performed, but it likewise had not improved the patient. In 1955 a third operation had been performed. This had consisted of emplacement of a fascial sling beneath the urethra, carried out through both abdominal and vaginal incisions. This measure had abated the incontinence very minimally.

We first saw this patient in June, 1958, at which time pelvic examination showed very slight relaxation of the scarred anterior vaginal wall. Rather marked urinary incontinence with stress could be corrected by elevation of the urethrovesical area. There was minimal uterine descensus, and an old laceration of the perineum was noted. Cystoscopic examination disclosed shortening of the urethra, mild urethritis, and some dilatation and scarring of the vesical neck suggesting previous surgical treatment. The capacity of the bladder was normal, without significant residual urine. With the bladder full the patient demonstrated marked stress incontinence. Results of routine urinalysis were within normal limits.

Operation was performed on June 16, 1958. The bladder was found to be densely adherent to the posterior aspect of the rectus muscle and to the posterior surface of the symphysis, so that sharp dissection was required for mobilization. The fascial sling could not be identified as such. However, there were relatively few adhesions involving the urethra itself, and it was our impression that the two previous suprapubic operations had concerned the anterior wall and neck of the bladder almost exclusively. Urethrovesical suspension was accomplished with the use of nonabsorbable sutures in the anterior vaginal wall lateral to the urethra, supplemented by the emplacement of plicating catgut sutures at the level of the neck of the bladder. At the time of dismissal on the fifteenth postoperative day the patient was completely continent. Excellent elevation and elongation of the urethra appeared to have been achieved. In a recent follow-up letter (2 years postoperatively) the patient said that she was "completely dry."

Case 6. A woman 70 years old, pregnant once and successfully delivered once, on Aug. 25, 1958, had undergone a Manchester operation performed elsewhere in which partial amputation of the cervix and anterior colporrhaphy for a large but apparently asymptomatic cystocele had been done. Although she had never had difficulties previously from this symptom, several days after the operation severe urinary stress incontinence developed which required the use of perineal pads constantly. Repeatedly, for periods of several months thereafter, she had taken perineal exercises with and without the use of a perinometer, but improvement did not ensue.

We first saw this patient in May, 1960. Results of a general physical examination were essentially negative, except for the pelvic findings. In addition to the site of the amputated cervix we noticed considerable shortening and scarring of the anterior vaginal wall. Our impression was that the incision made for the anterior colporrhaphy had not been carried well down beneath the urethra. A recurrent Grade 1 cystocele and a urethrocele and moderate uterine descensus were observed. The patient spurted urine at the slightest cough. This could be corrected by urethral elevation. Cystoscopic examination disclosed a bas-fond with moderate cystourethrocele. The urethra seemed shortened, and proximal funneling appeared to be present. There was no residual urine; the capacity of the bladder was normal; and there was no evidence of cystourethritis.

In May, 1960, retropubic urethrovesical suspension was performed with the use of nonabsorbable sutures. This procedure appeared to elevate and elongate the urethra adequately. A number of catgut sutures were placed over the lower anterior wall of the bladder, elevating and, to a certain extent, plicating the neck of the bladder. At the time of dismissal the patient appeared to have obtained an excellent result.

Case 7. A woman 71 years old, pregnant once and delivered successfully once, had undergone a total abdominal hysterectomy at the age of 51 years and anteroposterior vaginal repair at the age of 56 years. In January, 1959, the latter operation had been repeated, combined with what amounted to a Le Fort obliteration of the midportion of the vagina. Although the patient never had difficulties with involuntary loss of urine previously, immediately after this operation almost total urinary incontinence had developed, requiring the constant use of perineal protection. This incontinence had not abated with the practice of perineal exercises.

We first saw this patient in October, 1959. Pelvic examination disclosed almost complete obliteration of the vagina, with a small channel approximately 5 cm. in depth extending up the lateral sides of the vaginal tract. Slight urethrocele appeared to be present. Urine leaked at the

stress of the slightest cough or change in position. Cystoscopic examination disclosed nothing significant. Clinically, it appeared that the fused portion of the anterior and posterior vaginal walls, which terminated at the level of the midurethra, perhaps was exerting downward tension on the neck of the bladder and producing the incontinence.

On Oct. 29, 1959, the anterior and posterior vaginal walls were separated as far back as the apex of the vagina. The procedure was carried past the vault, and the uterosacral and cardinal ligaments were isolated on each side. An enterocele sac was not encountered. The ligaments were attached to the angles of the vaginal vault and approximated in the midline as well. The anterior vaginal wall was then dissected completely to the external urethral meatus, and the pubocervical fascia, the neck of the bladder, and the urethra were imbricated in the midline. Very satisfactory repair, with elevation of the urethrovesical area and restoration of the posterior angle, was accomplished. The vagina was reconstructed in the usual manner, although the resulting structure was narrowed and shortened considerably, as anticipated. The postoperative course was entirely uneventful, except for prolonged retention of urine; however, at the time of dismissal the patient was voiding normally and was entirely continent and remained so until the time of this writing.

Case 8. A woman 47 years old, pregnant once and successfully delivered once, had undergone multiple curettages for menometrorrhagia and, in March, 1950, vaginal hysterectomy for this problem. A history of urinary stress incontinence had not been obtained. In September, 1953, after a prolonged bout of urinary urgency, frequency, and dysuria, cystoscopic examination had disclosed a large urethral diverticulum situated in the floor of the urethra just to the right of the midline and 1 cm. distal to the vesical neck. This had been removed per vaginam on Sept. 3, 1953. At operation the tissues surrounding the diverticulum had been noted to be rather edematous and inflammatory. The entire diverticular sac had been excised, the opening in the urethral wall closed with two rows of 3-0 chromic catgut, and the vaginal wall closed with interrupted sutures of No. 1 chromic catgut.

Almost immediately after the operation profuse urinary stress incontinence had developed. Pelvic examination 2 months after the operation had disclosed only a moderate cystourethrocele. Cystoscopic examination had shown no evidence of urethrovaginal fistula, but only moderate relaxation of the entire floor of the urethra, with urethral shortening.

On March 2, 1954, the anterior vaginal wall was incised and the cystourethrocele was dissected, the dissection being carried far laterally and completely down to the external urethral meatus. A standard Kennedy type of repair was performed. Another cystoscopic examination 3 months later, performed because of the presence of recurrent urinary urgency and frequency, disclosed marked granular urethritis and trigonitis. There was no residual urine and the capacity of the bladder was normal. There was a small diverticulum in the left wall of the bladder. This patient has been seen on numerous occasions during the past several years. She continues to experience urinary frequency, minimal stress incontinence when the bladder is full, and some dribbling immediately after voiding. However, she appears to have excellent support of the bladder and urethra and does not wish to receive any additional treatment for the slight urinary incontinence. Periodically, since the last operative procedure, she has practiced perineal exercises with and without the perinometer.

Comment

It will be noted that all but one of the 8 patients reported upon were encountered within a few months, indicating that iatrogenic incontinence is not uncommon in our experience. Urethral shortening and funneling, scarring, fixation, and fibrous replacement of the smooth muscle of the neck of the bladder and proximal portion of the urethra appear to characterize the condition of all patients in this category.

In our experience, these changes most frequently have been the results of attempts at urologic manipulation (fulguration, dilatation, stretching) of the urethra for what have appeared to be, at least from the symptomatic standpoint, relatively trivial urinary disorders such as urethritis, dysuria, hesitancy, frequency, and postpartum or postoperative retention of urine. The patients in Cases 1, 2, 3, and 4 and probably the one in Case 5 are representative. In addition to the patients reported upon who had stress incontinence, we have seen a number with

urethrovaginal fistula or even total loss of the urethra resulting from fulguration of the neck of the bladder, the most recent fistula being in a 12-year-old girl.

Transurethral resection of the neck of the bladder in the female has become a much-favored procedure in certain sections of the country, series of cases numbering several hundred being reported. In other medical centers it is indicated that the necessity for this operation rarely arises. The latter coincides with our experience. Without question, some women who have obstruction of the neck of the bladder will be benefited by transurethral resection. This operation, when carefully accomplished and when patients are carefully selected for it, should be relatively innocuous. Perhaps our opinion is somewhat biased, since only those patients who obtained a poor result from resection (meaning those with fistula or urinary stress incontinence) will be encountered in a gynecologic practice. Nevertheless, our experience certainly suggests that transurethral fulguration of the neck of the bladder and stretching or dilatation of the urethra are contraindicated for patients who have retention of urine after parturition or various pelvic operations, especially if the latter have been done primarily for urinary incontinence.

Patients with postoperative retention of urine as a rule have some interference with urethrovesical dynamics, rather than a true mechanical obstruction. Under such circumstances urologic manipulation will only destroy the supports provided by surgical treatment or further attenuate the available contractile tissue constituting the neck of the bladder and proximal portion of the urethra. With patience and equanimity exercised by both the patient and the physician, and by the policy of dismissing some patients from the hospital with a retention catheter in place and instructing others who have a high residual urine in the technique of self-catheterization (as in our Case 1), time will correct all problems of postoperative retention of urine without the risk of either producing or perpetuating incontinence.

The same type of shortening, scarring, and fixation of the urethra with resulting urinary incontinence which appears after resection of the neck of the bladder also may be produced by extraurethral operative interference of many types. Most commonly these types of lesions follow removal of urethral diverticula (Case 8), repair of low-lying vesicovaginal or urethrovaginal fistulas (Case 2), or merely a poorly performed repair of a relatively asymptomatic cystocele (Case 6). Similarly, the plastic reconstruction of a destroyed urethra, even though anatomically successful, may not eradicate urinary incontinence. Even though the continuity of the urethral tube may be preserved or restored by an operative procedure, the patient may remain incontinent as a result of the inert noncontractile tissue composing the new urethra.

Much to the distress of both the patient and the physician, the operative correction of uterovaginal relaxation occasionally will produce urinary stress incontinence in a patient not previously affected by this symptom. Irrespective of the operation employed, whether it be vaginal hysterectomy with repair or the Manchester (Case 6) or Le Fort operation (Case 7) or partial vaginectomy, repair of a large cystocele and correction of uterine prolapse may so alter the position of the bladder that urinary stress incontinence will be the result.

In the presence of a large cystocele, increases in intra-abdominal and intravesical pressure will be transmitted largely to the most dependent portion of the cystocele (out the vaginal introitus), rather than against the attenuated urethrovesical junction. In addition, prolapse of the bladder, as it develops progressively, tends to angulate or to kink the urethra to a certain extent. Sometimes this action will "cure" the patient's incontinence or even overcompensate for the leakage in that the bladder must be elevated before the patient is able to void. Careful search of the history of many patients who have maximal prolapse (who are continent, as a rule) will disclose that they had stress incontinence at one time. Operative correc-

tion of the uterine prolapse and repair of the cystocele not only correct the urethral angulation but also direct any increases in intravesical pressure upon the atonic funneled neck of the bladder and urethra. When a patient has this type of condition, unless special effort and attention are given to the urethral area—meaning the same attention that would be given to the patient with a severe degree of stress incontinence—the end result may be that she will continue to be very wet and unhappy after repair of the cystocele and correction of the prolapse have been accomplished.

Recognition on the part of the physician that the various operative procedures mentioned may produce urinary stress incontinence should eliminate much of the problem. Fulguration and resection of the neck of the bladder should be performed only for very specific indications, with careful forethought of the risk involved. The patient who does not have incontinence but who presents with uterine prolapse and a large cystocele (classified by Ball as "potential incontinence") should have the benefit of the same detailed attention to the urethrovesical area which would be accorded the patient with severe incontinence. Furthermore, and of more importance, operation upon the patient who has an asymptomatic cystocele should be avoided. In the absence of concomitant urethral relaxation and urinary incontinence, cystocele alone is rarely if ever responsible for any symptoms. Certainly, the mere presence of a moderate cystocele is inadequate justification for surgical repair.

When the lower angle of a Le Fort wedge excision or repair of a subtotal vaginectomy terminates at the level of the neck of the bladder or midportion of the urethra, urinary incontinence sometimes ensues. Presumably this sequel results from the contraction and tension exerted on the urethra by the scar tissue at this level. For this reason and for many others, we consider the Le Fort operation to be obsolete. Similarly, vaginectomy is unnecessary in the management of uterovaginal prolapse or even prolapse of the vaginal vault. Rather than to shorten the vagina to the urethral level, it is preferable to assure equal support by constriction and narrowing of the vaginal vault or of the entire length of the vagina, provided preservation of vaginal function is not a paramount consideration. This measure will preserve sufficient vaginal depth so that an inordinate pull or excessive scarring will not occur at an area conducive to the production of urinary incontinence.

Summary

1. A little discussed cause of that type of urinary stress incontinence resulting from gynecologic and urologic operative procedures has been presented, with reports of representative cases.

2. In our experience, iatrogenic urinary incontinence most commonly has followed fulguration of the neck of the bladder performed for relatively trivial urologic symptoms. Although transurethral resection of the neck of the bladder may be helpful to the rare woman who has obstruction at this site, it is not an innocuous operation to be applied indiscriminately, and it definitely should be avoided when the patient has a recent history of operation for urinary stress incontinence.

3. Recognition by physicians that, unless special precautions are taken, urinary incontinence may be induced by various gynecologic operations should eliminate much of the problem.

4. At least 3 to 6 months should elapse between the causative procedure and any attempt to correct this type of urinary incontinence by surgical means.

5. As is true of the patient who has recurrent urinary incontinence, the patient who has iatrogenic urinary incontinence often will not be helped by simple vaginal operation or repetition of some vaginal procedure. Suprapubic urethrovesical suspension or a combined approach will be required, as a rule.

Vesicovaginal fistula

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THE uncontrollable appearance of urine in the vagina that follows delivery or a surgical gynecologic procedure is disconcerting to both the physician and patient. Because of the close anatomic relationship of the bladder and ureters to the generative tract, injury to these structures may be possible. This is particularly true if the structures are distorted by ovarian, tubal, or uterine tumors or inflammatory lesions. In the gynecologic patient, the increased incidence of total abdominal and vaginal hysterectomy makes urinary tract damage more prevalent. However, from the obstetric standpoint, a better understanding of dystocia, the application of proper indications and use of forceps, the employment of x-ray pelvimetry, and the earlier resort to abdominal delivery have contributed to the marked diminution of urinary tract accident. In a review covering a 25 year period at the Margaret Hague Maternity and Los Angeles County Hospitals in which 300,435 deliveries were studied, there was a dramatic reduction in the number of vesicovaginal fistulas in the latter years.[15] Of the 23 fistulas found in the entire study, 15 appeared after difficult forceps operations, 5 after spontaneous deliveries, 2 after breech extractions, and 1 after a cesarean section.

The present study is confined to vesicovaginal fistulas that follow gynecologic and obstetric procedures. According to Falk,[7] this type of fistula has been recognized since the beginning of recorded time. Because of the secondary status of women in the early days, obstetrics was entrusted to midwives who apparently had slight concern for the condition of the generative tract after delivery. The first written data about bladder fistula appeared in Hindu medical reports as early as 800 B.C. Hippocrates had mentioned the involuntary passage of urine but little was actually known about this lesion until the sixteenth century; then there followed a succession of informative literature. Finally, in 1852, Sims[25] published his classical thesis on the repair and care of vesicovaginal fistula. From that time on, considerable advance was made. Two comprehensive historical reviews have been published by Kelly[12] and Miller.[16] Numerous extensive studies have since appeared in the world literature.[4, 6, 8, 10, 13-15, 17, 21, 23, 24, 26-28] The continued progress in the evaluation and treatment of fistulas has been the result of increased knowledge of antisepsis, antimicrobial agents, and a wider understanding of the normal physiologic and abnormal pathologic process.

Because of the recent occurrence of vesicovaginal fistula in several of our cases, a study of this complication in the obstetric-gynecologic patient was made at the Sinai Hospital in Baltimore. This survey was conducted on 16,355 gynecologic patients and 27,456 obstetric deliveries that entered the hospital in a 9 year period from 1952 to 1960, inclusive. The purpose was to determine the number, cause, nature, treatment, and results in those patients who developed involuntary passage of urine from the vagina due to bladder injury that followed operation, pelvic genital malignancy, and delivery. The records revealed that 15 patients, in this period of time, entered the hospital for definitive treatment of vesicovaginal fistula (Table I).

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It has been generally accepted that the most common causes of urinary fistula formation are obstetric injury, surgical trauma, and genital malignancy or the use of x-ray and radium in the treatment of this malignancy.[7] Therefore, we correlated the fistulas found in our patients according to this classification.

From 1952 to 1960, inclusive, 27,456 patients entered the obstetric service of the hospital. There were 877 patients delivered by cesarean section; 15,355 had low forceps deliveries; and 1,591 patients had midforceps deliveries. A breech presentation was found in 1,293 patients of whom 1,250 were delivered per vaginam. All of the follow-up records failed to reveal one instance of urinary bladder fistula.

In the same period of time, 16,355 patients entered the gynecologic service for definitive surgical therapy. There were 205 patients who had a subtotal hysterectomy, none of whom had resultant bladder injury. Of the 1,458 patients who had a total hysterectomy, 9 subsequently developed bladder fistulas. There were 198 patients who had an anterior repair, 940 with anterior and posterior repairs, and 57 with Manchester operations, all without evidence of bladder injury resulting in fistula. In a group of 484 patients who were treated by vaginal hysterectomy, 2 were found later to have developed leakage of urine from the bladder into the vagina. The general policy used in the treatment of pelvic genital malignancy has become standard, with a few exceptions. The patients with invasive carcinoma are treated with radium and external radiation, while patients with carcinoma in situ have total hysterectomies. Where there is endometrial carcinoma, intracavitary radiation is followed in 6 weeks by total hysterectomy. Two of the patients who had received radium and external radiation for cervical malignancy developed bladder fistulas. There were no further bladder fistulas found in the 274 cases of carcinoma in situ, 129 of infiltrating carcinoma of the cervix, or in the 118 patients with endometrial malignancy.

Two of our 15 recorded cases of bladder fistula were in patients referred from the Urologic Service. Both of these patients had had bladder fulguration followed by vesicovaginal fistula and then by transvesical repair. Finally, one fistula was seen after a prolonged labor and difficult forceps delivery at another hospital (Table II).

Repair of fistula

The immediate repair of an operative or obstetric injury to the bladder or ureter, if detected, seems to be the manner of choice. Of 4 such bladder injuries, 2 following abdominal section and 2 following hysterec-

Table I. Gynecologic operations followed by vesicovaginal fistulas

Name	*Age*	*Procedure*	*Type of repair*	*Result*
J. K.	36	Vaginal hysterectomy	Electrocauterization	Cured
E. Z.	41	Midforceps, prolonged labor	None	Fistula
M. V.	10	Fulguration of vesicle neck	Transvesical repair	Cured
J. B.	49	Radium for carcinoma of cervix	Bricker	Cured
R. L.	50	Total hysterectomy for fibroids	Transvesical	Failed, repaired elsewhere.
R. M.	40	Radium for carcinoma of cervix	None	Fistula
M. M.	35	Vaginal hysterectomy for prolapse	Latzko	Cured
R. W.	52	Fulguration of bladder	Transvesical	Cured
K. E.	42	Total hysterectomy for fibroids	Vaginal repair	Cured
B. L.	45	Total hysterectomy for fibroids	Latzko	Cured
L. S.	41	Total hysterectomy for fibroids	Latzko (2)	Cured
Y. P.	48	Total hysterectomy for fibroids	Latzko (2)	Cured
A. D.	52	Total hysterectomy for dysfunctional bleeding	Latzko	Cured
L. S.	40	Total hysterectomy for fibroids	Latzko	Cured
E. S.	40	Total hysterectomy for dysfunctional bleeding	Latzko	Cured

Table II. Vesicovaginal fistulas in relationship to obstetric, gynecologic, and urologic procedures (1952 to 1960)

Type of case	*Operation*	*No.*	*Vesicovaginal fistula*
Obstetric	Cesarean section	877	0
	Midforceps	1,591	0
	Low-forceps	15,355	0
	Breech	1,293	0
	Spontaneous delivery	8,340	0
Gynecologic	Total abdominal hysterectomy	1,458	9
	Subtotal abdominal hysterectomy	205	0
	Anterior repair	198	0
	Anterior and posterior repair	940	0
	Vaginal hysterectomy	484	2
Uterine genital malignancy	Manchester operation	57	0
	In situ cancer of cervix	274	0
	Carcinoma of cervix	129	0
	Endometrial carcinoma	118	2
Urologic	Fulguration of bladder	523	2

tomy, healing occurred without urinary infection or residual fistula formation. This conforms with the experience of other gynecologic surgeons.[1-6, 8, 14, 17, 21, 24, 26, 27] Until recently the usual methods of treating vesicovaginal fistula discovered sometime after operation or delivery was to delay the repair for 3 to 6 months. In 1953, Collins and Jones,[2] taking advantage of the anti-inflammatory properties of cortisone, began preoperatively treating patients with vesicovaginal fistula. By this means they were able to operate upon these patients without the prescribed waiting period. For 6 years, 9 such patients were so treated with immediate cures observed in 8 of them. The work was continued by Collins, Pent and Jones[3] so that in a series of 21 cases, 15 were closed successfully after the first attempt.

Our experience with anti-inflammatory drugs, specifically phenylbutazone and oxyphenylbutazone, has been rather extensive. It is possible that the same results could be obtained with the preoperative use of these drugs without the hazard of large doses of cortisone. However, because of the sparsity of cases of vesicovaginal fistula on our service, the opportunity to use antiphlogistic agents has been limited. Up to this time we have adhered to the doctrines which were advocated by Ball,[1] Everett and Mattingly,[6] Falk,[7] Moir,[17] Sims,[25] and others. In the future, we would not be averse to attempt an early repair with the preoperative administration of anti-inflammatory agents.

Whether immediate or delayed repair is contemplated, the origin of vaginal urinary drainage must first be determined. At times it may be difficult to decide whether the leakage is the result of a traumatic opening into the bladder or whether the cause is urethral in origin. The use of retrograde cystoscopy and pyelography, intravenous pyelography, and the employment of intravenous and intravesical dyes may be necessary to establish a correct diagnosis. Retrograde cystoscopy by the indirect method could be difficult if there is a large opening in the bladder, thus preventing proper filling.

The majority of gynecologic and urologic surgeons stress the importance of removing all infection and necrotic tissue about the fistula before operation.[27] In the absence of anti-inflammatory agents, the removal usually takes from 3 to 6 months. During this time medications are used to acidify the urine thus inhibiting the formation of urinary concretions and vaginal inflammation. An operation is attempted only when all reaction has subsided and the tissues have

returned to normal consistency and mobility.

Ball[1] lists at least 25 surgical principles in undertaking bladder fistula operations. In general, they include attention to all factors concerned with the union of tissues. This means an evaluation of the patient's health, care to relieve local infection, and the deposition of urinary salts about the edges of the fistula. The elimination of the possibilities of upper and lower urinary tract infection is also essential. In addition to the generalizations, we should consider specific factors such as the accessibility of the fistula, the best position for the patient on the operating table, and the type of approach to the operative field. Finally, a study must be made as to the adequate exposure of the fistulous tract and whether vaginal or perineal incisions may be necessary. The proper dissection of the tissues about the operative site, the correct placement of the sutures without undue tension, and an outline of acceptable postoperative care should be considered before operation takes place.

The methods of repair of a vesicovaginal fistula have been varied. They have now been resolved into one of 5 procedures, as follows: (1) electrocauterization, (2) the use of pedicle flaps of muscle, labium, uterus, or cervix, (3) suprapubic transvesical transabdominal approach, (4) transplantation of the ureters into the intestine or into a cecal pouch, and (5) vaginal procedures.

Most gynecologists, since the time of Sims,[25] have used the vaginal approach. In contrast, most urologists rely upon the transvesical or transabdominal operation. Dorsey,[4] Graham,[10] O'Conner,[18] Schneiderman and Strean,[24] and others are the chief proponents of the abdominal technique. In a recent study, Roen[23] recommended a combined vaginal and transvesical repair of bladder fistula. The transplantation of ureters is rarely done except in patients with infiltrating inoperable genital or bladder carcinoma.

An excellent method devised for the correction of minute fistulas is that of electrocauterization. A small insulated wire is placed through the vesical opening and the current is applied for 10 seconds. Frank,[9] O'Conner,[18] Ottow,[19] Peterson,[20] Quinby,[22] and Zabrowski[29] have reported satisfactory results with that technique.

Three types of vaginal procedures are described by writers on this subject. The Sims operation consists of paring the edges of the fistula and closing the defect in one layer, either with absorbable or with nonabsorbable suture material. A second method is that of closing the pared area in layers. The bladder is closed so that it is water-tight. The vagina is then sutured in layers over the fistula. In 1956, Moir[17] reported his personal experience with this method in 136 cases where there was adequate closure in all but 2. He emphasized the possibility of simultaneous fistulas. If a fistula is of long standing, the presence of vesical calculi must be considered.

Vesicovaginal fistulas that follow total abdominal hysterectomy differ from other abnormal openings into the bladder. After the complete removal of the uterus, the abnormal opening is usually high in the vault of the vagina. Because of the inaccessibility and fixation of tissues, operation by the vaginal route was considered difficult. Prior to Latzko's work in 1913, these lesions were repaired by the transvesical method; this is sometimes done even today. By 1942, Latzko[13] had reported 31 patients who were treated by partial colpocleisis, 30 of whom had been cured. Holden[11] and Falk and Bunkin[8] were enthusiastic advocates of this operation. In 1956, Everett and Mattingly[6] described 43 cures by the Latzko technique and 12 by other procedures.

The methods used to repair the fistulas in our cases proved to be interesting. Two patients were discharged from the hospital without operation. One patient had advanced generalized carcinomatosis; she was transferred to a nursing home. The other had entered the hospital following a prolonged labor and difficult delivery at another institution. In this instance, the fistula was so minute in character that no treatment was advised by the attending physician. Electrocauterization followed by a cure was used in the patient with a small fistula that appeared

after a vaginal hysterectomy. Three patients were seen on the urologic service. Two of them had transvesical repairs; they were cured. The third, who had extensive involvement of the bladder because of cervical malignancy, was treated by transplantation of the ureters into a cecal pouch. On the gynecologic service, one patient had a Sims operation; the result was not effective. Subsequently, the fistula was successfully closed by the Latzko operation. The remaining 8 patients were cured by partial colpocleisis; 6 after the initial attempt and 2 as secondary procedures.

Summary

The methods selected for repair of urinary vesical fistula have been a matter of discussion even prior to Sims. From our study, it is apparent that the most satisfactory operation for adequate repair of the fistula that follows total abdominal hysterectomy is that of partial colpocleisis. What may appear to be a formidable procedure is simplified by adequate exposure and adherence to the technique described by Latzko. The prophylactic precautions in the prevention of fistula of the bladder while performing any gynecologic operation are the points to be emphasized. The careful and meticulous attention during the removal of the bladder from the uterus, cervix, and vagina as well as the reperitonization process is far more important than the mastery of a specific method of repair.

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Retroperitoneal tumors in gynecology

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TUMORS which originate primarily in the retroperitoneal space are infrequently encountered in gynecologic practice except when they occur as pelvic masses. As such, they are often diagnosed as tumors of the reproductive organs, and the patient is operated upon under this assumption. The error may be compounded at operation. When an obvious retroperitoneal tumor is discovered at the time of laparotomy, either radical removal is not attempted because of the proximity and possible involvement of vital structures, or, in attempting a removal without adequate preoperative preparation, the surgeon runs the risk of inadvertently injuring a major structure such as large blood vessels, ureter, or bowel.

The intent of this report is to review the surgical and clinical findings in 14 cases of retroperitoneal tumor for the purpose of calling attention to this type of pelvic tumor, to discuss techniques which may be helpful in the preoperative diagnosis, and to demonstrate some of the pitfalls which may be met when these tumors are encountered on a hospital gynecologic service.

Material

On the gynecology service of the University of California School of Medicine, San Francisco, during the years 1939 to 1959, 14 patients were operated upon for tumors which proved to be retroperitoneal. A synopsis of each case is presented in Tables I and II.

Of the 14 tumors, 5 were benign and 9 were malignant. Not included are 3 retroperitoneal masses which were found at operation to be pelvic kidneys.

In 7 of the 14 cases, the tumor was discovered during routine pelvic examination, the patients being essentially asymptomatic. In the remaining 7, the initial complaints were abdominal pain or distention in 3 patients, edema of the lower extremities in 2, backache in one, and weight loss, fever, and fatigue in one. The majority of patients with malignant growths had symptoms which could be related to the tumor. On the other hand, all the patients with benign tumors were asymptomatic.

The most frequent preoperative diagnosis was that of ovarian neoplasm, which was made in 7 of the 14 cases. Pelvic abscess, abdominal carcinomatosis, and intraligamentous myoma each were diagnosed once. In only 4 cases was a diagnosis of retroperitoneal tumor seriously considered.

At operation major blood vessels were inadvertently entered in 3 of the patients with malignant retroperitoneal tumors and in one with a histologically benign but inoperable tumor mass. In 2 of these patients, massive hemorrhage occurred during the surgical procedure, requiring extraordinary measures for control and placing each patient in an extremely precarious condition.

All the patients with benign retroperitoneal tumors are alive and well whereas all but 2 of the patients with malignant neoplasms died within 2 years of the time the diagnosis was made.

Anatomy and pathology

The retroperitoneum is, in some areas, an actual space; in others it is only poten-

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Table I. Benign retroperitoneal tumors

Case No.	*Age (years)*	*Initial complaint*	*Preoperative diagnosis*	*Pathologic diagnosis*	*Clinical features*	*Outcome*
1	59	Stress incontinence	Ovarian cyst	Lipoma	5 by 8 cm. sausage-shaped mass, left adnexal region on pelvic examination. Retroperitoneal in iliac and obturator fossae at laparotomy. Surgically excised.	No recurrence
2	39	Hot flashes	Metastatic cancer to right overy	Leiomyoma	History of subtotal hysterectomy for fibroids. Radical mastectomy 3 years previously for small cancer of breast. Nontender, fixed, 12 cm. mass in right adnexa on pelvic examination. Large, firm, slightly bosselated mass in right obturator fossa with no attachment to cervical stump, round ligament, or ovary. Excised.	No recurrence
3	17	Pregnancy	Neurofibroma (after transvaginal biopsy)	Ganglioneuroma	6 by 7 cm., hard, nontender, fixed mass in left sacrosciatic notch discovered at prenatal examination. Delivery at term by cesarean section. Surgical excision at laparotomy 3 months postpartum.	No recurrence
4	29	Miscarriage	Possible retroperitoneal tumor	Paraganglioma	20 by 15 by 15 cm. mass occupying left lower abdominal quadrant on pelvic examination following complete spontaneous abortion. Laparotomy with attempt to remove huge mass extending from pelvic brim to diaphragm and extending across midline. Massive hemorrhage controlled by packing and closing. Second attempt at removal in Midwest hospital 12 years later; incomplete. Postoperative x-ray therapy.	Alive and well 2 years after x-ray therapy. Small tumor mass palpable.
5	26	Pregnancy	Presacral dermoid	Benign cystic teratoma	6 by 6 by 7 cm. slightly irregular, soft, cystic mass anterior to third, fourth, fifth sacral segments, posterior to rectum on prenatal pelvic examination. Delivery at term by cesarean section. Excision of mass via parasacral approach 3 months post partum.	No recurrence

tially a space unless it contains a mass.[11, 12, 18] In addition to such major organs as the kidneys, adrenals, and pancreas, and certain portions of the small and large bowel, the space contains the abdominal aorta and its branches, the inferior vena cava and its tributaries, the ureters, the autonomic nerves, and the branches and plexuses of the various spinal nerves. It is also richly abundant in fatty areolar tissue as well as lymph nodes and vessels. That this particular region also contains embryologic remnants of the urogenital ridge is sometimes thought to be of particular significance in the histogenesis of certain of the primary retroperitoneal tumors.[8]

Over 20 years ago, Brady,[3] in a study of various retroperitoneal conditions in women, described puerperal parametritis with abscess formation, and, in addition, noted 4 instances of unusual lesions—a fibromyoma of the urachus, a pelvic kidney, a mesenteric cyst, and a retroperitoneal chylous cyst. In the same year, Miller[10] tried to formulate

a classification of the retroperitoneal tumors most often encountered by the gynecologist but gave up because of the large variety of tumors which were possible. He compromised by stating the need for the gynecologist to know well the anatomy of this region and to understand thoroughly the various pathologic processes.

Ackerman[1] recently proposed a classification encompassing the many different types of tumor which originate in the retroperitoneal space. He was quick to point out that this classification merely demonstrates the many different types of tissues found in the retroperitoneal space but, because it does this so eloquently, his tabulation is reproduced here (Table III). Theoretically, at least, any one of these tumors may arise in or near the pelvis and thus come to the attention of the gynecologist.

In children, the principal lesions to be considered, by reason of their statistical incidence, are neuroblastomas, Wilms tumors of the kidney, and teratomas.[2] In the adult, lymphomas, liposarcomas, and rhabdomyosarcomas are the most frequent.

Diagnosis

The preoperative diagnosis of a retroperitoneal mass in the pelvis is not easy, as evidenced by the failure to entertain the possibility in 10 of the 14 cases presented here. This oversight, in retrospective analysis of these cases, could be traced directly to tunnel vision on the part of the attending physician —that is, an unwillingness or disinclination to consider the possibility that a pelvic mass may be anything other than a tumor of the reproductive tract. This, of course, is related to the fact that the gynecologist is oriented to think chiefly in terms of the uterus, tubes, and ovaries as the source of most tumors arising in the pelvic and abdominal regions within reach of the fingers of the examining hand. When a tumor is discovered in the female pelvis, the gynecologist is apt to assume that it originates in one of these structures unless concomitant symptoms implicating another organ system are present.

Actually, symptomatology is not too helpful in making a diagnosis of the retroperitoneal tumor. As in ovarian neoplasms, the onset is usually insidious. Because in the early stages of their developement such tumors do not involve the major organ systems, frequently there are no definitive functional symptoms. This is graphically illustrated by the group of patients presented in this discussion, half of whom had pelvic masses which were discovered during the course of routine pelvic examinations. The detection of a large pelvic mass rarely is a problem but determining whether the mass is intraperitoneal or extraperitoneal in location is often difficult. The extraperitoneal tumors palpated on bimanual examination often appear to arise directly from the lateral or posterior wall of the pelvis and cannot be separated from it by the examining finger. Usually they are fixed and relatively non-



Fig. 1. Medial displacement of the ureter by a large lymphosarcoma arising from the retroperitoneal space of the right hemipelvis (Case 8).

Table II. Malignant retroperitoneal tumors

Case No.	*Age (years)*	*Initial complaint*	*Preoperative diagnosis*	*Pathologic diagnosis*	*Clinical features*	*Outcome*
6	37	Abdominal distention, nausea, diarrhea	Ovarian carcinoma	Lympho-sarcoma	Ascites. Uterus displaced to left by hard tender mobile mass in right adnexa. Laparotomy and biopsy of retroperitoneal mass.	Died 19 days postoperatively
7	67	Abdominal swelling, fatigue, anorexia	Abdominal carcino-matosis	Lympho-sarcoma	Nodularity in region of left utero-sacral ligament. Abdomen distended with evidence of ascites; no definite mass. Laparotomy and biopsy of 25 by 15 by 10 cm. retroperitoneal mass. X-ray therapy; triethylene-amine.	Good palliation for 2 years. died.
8	57	Swelling of right leg	Intraligamentous myoma	Lymphoblastic lympho-sarcoma	Stony hard mass occupying right adnexal region, believed attached to and displacing uterus to left. Attempted surgical excision of large retroperitoneal mass occupying right hemipelvis. Common iliac artery and vein severed; rent in inferior vena cava with massive hemorrhage. Ureter intentionally sectioned to gain exposure for hemostasis. Estimated blood loss 10,500 c.c. Hemostasis by clamps and packing left in situ. X-ray therapy.	Good collateral circulation to right leg; necrosis of small area of heel. Alive and well 27 months postoperatively.
9	46	Low backache pain radiating to right leg; dysmenorrhea; dyspareunia	Ovarian tumor	Hodgkin's lymphoma	8 to 10 cm. fixed, rubbery, ovoid tumor in right adnexal area. Laparotomy with biopsy of retroperitoneal tumor occupying obturator and iliac fossa. Hypogastric vein inadvertently entered. Hemostasis by suture. X-ray therapy; nitrogen mustard.	Developed epigastric mass. Died 10 months postoperatively.
10	23	None	Ovarian tumor	Lipo-sarcoma	Hard, fixed mass in right adnexal area found on routine postpartum examination. Nonfunctioning kidney on IVP. Laparotomy elsewhere; retroperitoneal mass biopsied, interpreted as inflammatory tissue. Intensive antibiotic therapy; cortisone with subsequent febrile course; anorexia, fatigue, weight loss. Reoperation 2 months later revealed extensive retroperitoneal tumor in right iliac fossa, enveloping iliac vessels. Rebiopsied.	Hectic, febrile postoperative course. Died 25 days postoperatively.
11	18	None	Ovarian tumor	Hemangiosarcoma	12 cm. mass in right adnexa found on routine premarital examination. Laparotomy revealed large extremely vascular tumor arising from right iliac and obturator fossae, bulging into right broad ligament, displacing ureter anteriorly. Biopsied. Deep x-ray therapy (4,500 r tumor dose in 61 days) resulted in gradual shrinkage of mass. Reoperated with excision of mass 5 months after initial operation.	Died 5 months after second operation with frozen pelvis, bowel obstruction, uremia. Autopsy revealed extensive pelvic fibrosis. No evidence of tumor.

Table II—Cont'd

Case No.	*Age (years)*	*Initial complaint*	*Preoperative diagnosis*	*Pathologic diagnosis*	*Clinical features*	*Outcome*
12	57	Swelling and pain right leg	Probable carcinoma of ureter	Carcinoma of ureter	Treated for thrombophlebitis with prolonged course despite anticoagulants. IVP because of subsequent hematuria revealed nonfunctioning right kidney. 10 by 12 cm. hard, fixed mass attached to right pelvic sidewall then found on pelvic exam. Ureteral obstruction at 5 cm. on retrograde study. Laparotomy revealed 6 by 8 by 12 cm. mass involving cecum and terminal ileum, liver metastases. Ileotransverse colostomy and biopsy of mass.	Died 4 months postoperatively
13	44	Weight loss, fever, fatigue	Pelvic abscess; carcinoma in situ of cervix	Metastatic squamous carcinoma of cervix	Right leg swollen for 2 months. Cervical erosion with bleeding on contact; "anterior-cone" biopsy interpreted as carcinoma in situ. No parametrial induration. Hard, nodular mass arising from right lateral pelvic sidewall. Laparotomy revealed mass in right iliac fossa extending into base of broad ligament. Biopsied; hypogastric vein inadvertently entered and repaired. Radium and deep pelvic x-ray therapy.	Died 11 months postoperatively
14	59	Abdominal pain	Ovarian carcinoma	Undiagnosed	Large, hard tumor mass filling pelvis and compressing rectosigmoid. Laparotomy revealed large retroperitoneal mass incorporating lower two thirds of sigmoid and rising above bifurcation of aorta. Not biopsied because of vascularity. Cecostomy.	Died 10 months postoperatively

tender. Occasionally they are situated so deeply within the true pelvis, as in Case 5, that it seems impossible that they may arise from within the peritoneal cavity. Mild edema, varicosities of a lower extremity, or atypical thrombophlebitis which does not respond to the usual therapy may be the only clue to suggest that the tumor is truly retroperitoneal. The urologist, also, despite his precision instruments and methods, has difficulty in the diagnosis of retroperitoneal masses.[15]

X-ray studies provide the best means available, aside from operation, for substantiating the retroperitoneal location of a tumor. Of greatest value are x-ray studies of the urinary and gastrointestinal tracts, but special views are required frequently to define these masses. Oblique and lateral projections often are of great value in the localization of a given tumor and should be requested whenever a retroperitoneal tumor is suspected. Lowman and Davis[9] stated that careful analysis of the results of these examinations may yield an extensive amount of information. These relatively simple techniques should always precede the use of direct radiographic methods such as retroperitoneal pneumography, aortography, and venography. These authors also pointed out that intraperitoneal masses seldom produce renal displacement until they are very large, whereas relatively small retroperitoneal tumors may displace a kidney or ureter. Schulte and Emmett[13] found renal and ureteral displacement in 72.5 per cent of pa-

tients with retroperitoneal tumors. Medial or anterior displacement of a ureter strongly suggests a retroperitoneal mass, as exemplified in Case 8. In this patient, as shown in Fig. 1, the ureter was displaced medially by a large lymphosarcoma fixed to the right lateral pelvic sidewall. Compression and displacement of the urinary bladder to an anterior or lateral position may also be seen, as occurred in Case 11. In this instance the tumor was a large hemangiosarcoma occupying the right side of the pelvis (Fig. 2).

Intravenous pyelograms were obtained in 8 of our cases; in 6 they demonstrated significant displacement of the kidneys, ureter, or bladder, or nonfunctioning kidneys due to complete ureteral obstruction by the tumor mass. In the remaining 2 cases, pyelography showed no abnormalities. In one of these patients (Case 5), however, a mass was palpable on physical examination, a presacral teratoma deep in the pelvis, anterior to the third, fourth, and fifth sacral vertebra, and well below the major portion of the urinary tract. X-ray studies utilizing barium enema in this patient showed forward displacement of the rectum, a finding which is diagnostic of the retroperitoneal location of a mass. Lowman and Davis[9] stated that the barium contrast studies of the gastrointestinal tract may show only the size and relative location of a mass and not shed any light on the intraperitoneal or extraperitoneal location. Barium contrast studies in Case 11 showed displacement of the sigmoid colon by a large retroperitoneal mass (Fig. 3) and the outlining of a retroperitoneal tumor by small bowel shadow in Case 8 (Fig. 4). Either of these pictures might have been produced by large adnexal tumors. Therefore, any interpretation of barium studies must be made in the light of additional clinical and laboratory findings, as well as other special radiographic techniques when indicated.

The direct radiographic methods of aortography, venography, and retroperitoneal pneumography may be useful in defining the location of pelvic tumors. The technique of venography, as described by Dalali and associates,[6] involves the injection of contrast medium (Neo-iopax) into the femoral or saphenous vein and the application of abdominal pressure just below the umbilicus. If a major vessel is obstructed, the collateral circulation will indicate the nature and location of the obstructing lesion. Steinbach and

Table III. Classification of retroperitoneal tumors (according to Ackerman*)

- **I. Tumors of mesodermal origin**
  - *A. Tumors arising from adipose tissue*
    1. Benign—lipoma
    2. Malignant—liposarcoma
  - *B. Tumors arising from smooth muscle*
    1. Benign—leiomyoma
    2. Malignant—leiomyosarcoma
  - *C. Tumors arising from connective tissue*
    1. Benign—fibroma (not reported)
    2. Malignant—fibrosarcoma
  - *D. Tumors arising from striated muscle*
    1. Benign—rhabdomyoma (not reported)
    2. Malignant—rhabdomyosarcoma
  - *E. Tumors arising from lymph vessels*
    1. Benign—lymphangioma
    2. Malignant—lymphangiosarcoma (unknown)
  - *F. Tumors arising from blood vessels*
    1. Hemangioma and angiosarcoma
    2. Hemangiopericytoma, benign and malignant
  - *G. Tumors arising from primitive mesenchyme*
    1. Myxoma—myxosarcoma
  - *H. Tumors of uncertain origin*
    1. Xanthogranuloma
- **II. Tumors of neurogenous origin**
  - *A. Tumors of nerve sheath origin*
    1. Nonencapsulated neurofibroma
    2. Encapsulated neurilemoma
    3. Malignant schwannoma
  - *B. Tumors arising from sympathetic nervous system*
    1. Ganglioneuroma
    2. Sympathicoblastoma
    3. Neuroblastoma
  - *C. Tumors arising from heterotopic cortical adrenal and from chromaffin tissue*
    1. Carcinoma arising from cortical adrenal tissue
    2. Malignant nonchromaffin paraganglioma
    3. Paraganglioma
    4. Functioning pheochromocytoma
- **III. Remnants of renal blastema**
- **IV. Tumors arising from embryonic remnants**
  - *A. Benign and malignant teratomas*
  - *B. Chordomas*
- **V. Metastatic malignant tumors**

*Taken from Ackerman[1] by permission of the author and of the Armed Forces Institute.

Smith,[14] using retroperitoneal pneumography, have found extraperitoneal masses arising from the pelvis; however, their technique is more applicable to outlining the adrenal glands.

With an increased awareness of the possibility of a retroperitoneal tumor and the use of appropriate radiographic studies, a positive preoperative diagnosis can be made in 60 to 65 per cent of patients.[6, 13]

Even after a mass has been localized in the retroperitoneum by radiographic techniques, the specific nature of the tumor usually cannot be determined until laparotomy and frequently not until the tissue has been examined microscopically.

Treatment

Prompt, complete surgical removal is the preferred method of treatment for most retroperitoneal tumors. The surgeon must be prepared to engage in a radical operation, and in many instances he will be wise to include a bowel preparation and ureteral catheterization in the preoperative preparation of the patient. Because of the vascularity of many of these tumors and frequent involvement of large blood vessels, Tidrick and Goldstein[17] recommend having vascular instruments available, including clamps for interruption of the aorta, inferior vena cava, and other large vessels, as well as vascular graft material. The availability of an almost unlimited supply of blood, together with equipment for intra-arterial transfusion in the event of massive hemorrhage, also seems advisable. Direct intra-aortic transfusion, as described by Collins,[4] may prove lifesaving in this circumstance.

Because the retroperitoneal space is relatively inaccessible, adequate exposure is of paramount importance if surgical extirpation is to be attempted. The incision, therefore, must be ample, whether longitudinal or transverse.

Because radiation therapy is the preferred treatment for lymphomas, the type of tumor should be established by microscopic examination of a frozen section before the surgeon proceeds with a radical operation. If this



Fig. 2. Compression and displacement of the urinary bladder by a retroperitoneal hemangiosarcoma arising from the right side of the pelvis (Case 11).

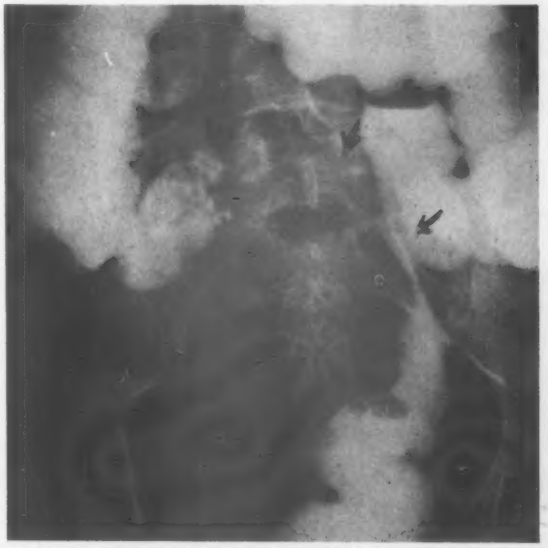


Fig. 3. Displacement of the sigmoid colon by a large hemangiosarcoma arising retroperitoneally in the right hemipelvis (Case 11).



Fig. 4. Outlining of a large retroperitoneal lymphosarcoma by small bowel shadow on barium enema examination (Case 8).

policy had been followed in Case 8 in this group of patients, undoubtedly a near catastrophe would have been avoided and the patient's subsequent course considerably simplified.

Widespread involvement, particularly of vital structures, also precludes a definitive surgical approach. It is quite likely that a proper assessment at the time of surgical exploration in Case 4 would have revealed involvement of the celiac axis and the folly of a direct surgical attack on the tumor.

Both of these patients were operated upon by relatively inexperienced surgeons, which serves to emphasize the need for mature judgment and great experience on the part of a surgeon who operates upon patients with retroperitoneal tumors.

Some of these neoplasms, even though characteristically radioresistant, will respond to radiation therapy. As a result of such treatment, an inoperable tumor may become operable. In other instances, good palliation can be achieved by surgical removal of all tumor tissue possible and postoperative x-ray therapy.

Prognosis

Benign retroperitoneal tumors are cured by surgical excision. However, most primary retroperitoneal tumors are malignant, as evidenced by Donnelly's series[7] in which 91 per cent were malignant and by Pack and Tabah's cases[11, 12] with an incidence of 86 per cent malignancy. These malignant tumors usually represent various types of sarcoma, with the lymphomas as a group the most frequently encountered type. Four of the 9 malignancies in the cases summarized in the present report fall into this category.

Because these malignant tumors develop insidiously in a relatively inaccessible area of the body, their recognition is usually delayed and their removal is often incomplete. The ultimate prognosis, in general, is poor, although effective palliation is possible in many cases, either through repeated surgical excision, as in the case of low-grade liposarcomas, or by means of radiation therapy, which is especially effective in certain of the lymphomas. In the present series the only patient with malignant disease who survived more than 2 years has a lymphosarcoma which has been controlled with deep x-ray therapy and when seen last, 27 months following the diagnosis and treatment, was free of symptoms. Unfortunately, the only patient with a malignancy which was resectable (Case 11) died of the late effects of preoperative radiation therapy—treatment which made possible the definitive surgical approach which would have resulted in a cure.

Summary

A great variety of tumors are found in the retroperitoneal space, many developing primarily from retroperitoneal tissues and others representing metastases from disease elsewhere in the body. Although no single type is seen frequently, such tumors are not rare, and the gynecologist should be alert to their possible occurrence.[16]

The clinical and surgical findings in 14 cases of retroperitoneal tumor (5 benign and 9 malignant) encountered on the gynecology service of the University of California School of Medicine during a 20 year period are discussed in this report. The important factors, as illustrated by these cases, are as follows: Diagnosis of retroperitoneal tumors is difficult, but, with increasing awareness of their incidence and the use of improved

radiographic techniques, the physician can diagnose most retroperitoneal tumors preoperatively.

Once the diagnosis has been established, preparations for radical surgical excision should be made in the expectation of finding a malignant lesion. Frozen sections should be examined histologically to determine the specific type of tumor. Except for lymphomas, the preferred treatment is surgical excision. Wide operative exposure is a prime requisite because of the relative inaccessibility of the retroperitoneum and the intimate relationship between these tumors and major vital structures. During the operation, keen judgment and skill are required to obviate serious accidents. Radiotherapy may be of value in the treatment of inoperable or incompletely resected tumors, since radiation often results in sufficient shrinkage of the technically inoperable mass to allow a surgical approach. If the process is malignant, the prognosis is poor, but it can be improved by more accurate preoperative diagnosis, better preoperative preparation, and wider surgical excision.

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Combined roentgenologic and gynecologic approach to evaluation of pelvic extragenital tumors of the female

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NEOPLASTIC and other masses in the female pelvis most frequently have a genital origin. This large group of tumors has received so much emphasis in the literature that the possibility of a nongenital origin may be scarcely considered in the preoperative evaluation. Yet, knowledge of the origin and extent of such a mass, and its effect on the surrounding structures, is of great value in planning adequate therapeutic measures as part of a systematic diagnostic evaluation. The gynecologist should seek competent radiologic assistance and use it to best advantage. The radiologist can often suggest the etiology of nongenital pelvic tumors and recommend further appropriate roentgenologic procedures to be correlated with other clinical data. This will be more frequently true if the radiologist is fully acquainted with the clinical picture. A combined approach by the gynecologist and his radiologic consultant will prove very efficient in eliminating unnecessary procedures or a poorly planned laparotomy.

Lever[1, 2] in 1842 recognized the obstetric importance of these masses; Lovelady and Dockerty[3] in 1949 reviewed the subject. Many types of nongenital pelvic masses occur. A convenient classification is given in Table I. The types encountered and their relative frequency are also indicated.

The radiologist has certain general criteria which enable him to recognize or at least to suspect the extragenital origin of a pelvic mass. In summary these are:

1. Association of the pelvic mass with a large retroperitoneal mass, indicating primary retroperitoneal disease with extension into the pelvis (Case 3).
2. Evidence of generalized abdominal disease (Case 14).
3. Bone lesions (primary or metastatic) protruding into the pelvis (Case 4).
4. Primary lesions in the urinary tract (Cases 5 and 11).
5. Primary gastrointestinal tract lesions (Cases 7, 8, and 9).
6. The association of pulmonary or mediastinal disease (Case 15).
7. Typical soft tissue abscess (Case 8).
8. Primary lesion elsewhere that frequently metastasizes to pelvis (Case 10).
9. Calcification of characteristic pattern (Case 2).

The purpose of the present study is to elaborate and re-emphasize the importance of roentgenologic aids in the nongenital

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pelvic mass in the female and the diagnostic dilemma it often presents.

Material and methods

The source of the case material used in this study was the files of The University of Texas M. D. Anderson Hospital and Tumor Institute. No attempt was made to review completely all such cases seen; the paper presents illustrative cases to emphasize certain principles regarding the value of radiographic investigation. The radiologic records of approximately 800 female patients registered from July 1, 1944, to June 30, 1959, each of whom was known to have an extragenital mass, were reviewed. One hundred and forty-nine cases were found in which the primary problem on admission was an undiagnosed pelvic mass and in which roentgen investigation was a most important factor in evaluation. These were reviewed in detail, and 15 cases of more than usual interest and instructive value were selected for presentation.

Thus, of the 800 cases initially considered the 149 forming the basis of this study satisfy the following criteria:

1. Palpable pelvic mass as the presenting problem.
2. Adequate radiologic investigation.
3. Adequate clinical and pathologic confirmation.

Roentgen procedures

In all cases a chest film is obtained, even if only for preoperative evaluation. This, along with a plain film of the abdomen, may be all that is necessary for a diagnosis of a mass of extragenital origin, and occasionally it suffices for a histologic diagnosis. An exploratory laparotomy may thus be rendered unnecessary; in any event, more appropriate therapy may be planned.

The types of radiographic examination utilized in this series are listed in order of frequency: (1) plain film of the abdomen (usually a part of pyelography); (2) excretory pyelography (routine in patients with pelvic mass); (3) barium enema; (4) small bowel study; (5) retrograde pyelography.

More specialized roentgenographic procedures such as intra- or retroperitoneal gas injection or vessel opacification are seldom required. They usually add little information, though this is not always so (Cases 12 and 13).

Case reports

Case 1. M. S. was a 23-year-old white woman, gravida iii, para ii. Six years before admission she had suffered from pain of minor degree in the left leg. Pelvic examination revealed a firm 8 cm. mass projecting into the introitus on the left. Roentgenograms of the pelvis revealed an osteochondroma of the ilium, confirmed at biopsy. Pregnancy occurred, and treatment was delayed until delivery was successfully accomplished by cesarean section. Subsequent resection of the lesion was incomplete because of shock which supervened during the operation. Following recovery, the patient refused further surgical procedures. One year later, the size of the residual tumor increased and further radiographs were interpreted as showing chondrosarcoma (Fig. 1). Biopsy confirmed the malignant nature of the lesion. A hemipelvectomy was performed. Two small recurrences have since been excised. The patient has been otherwise well for the past 9 years.

Case 2. B. M. was a 68-year-old white woman, gravida i, para i. The history of this patient was one of removal of a "grossly malignant ovarian tumor" 9 years prior to admission and gradually increasing abdominal distention for the past 6 years. There was a 12 cm. pelvic mass and a similar epigastric mass. Paracentesis yielded copi-

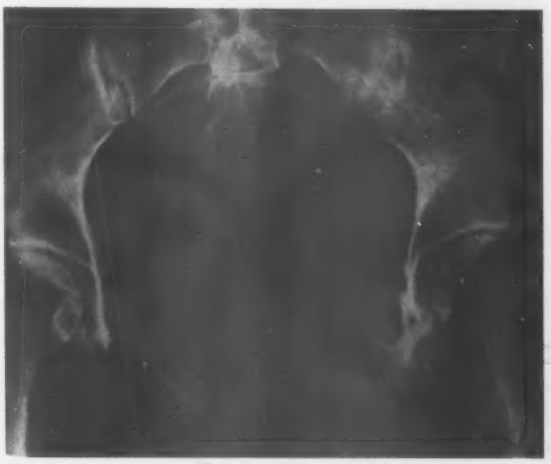


Fig. 1

ous fluid on numerous occasions. Despite the fact that all cell blocks were negative for tumor, the history and clinical course led to treatment with radioactive colloidal gold. This was without effect. Plain films of the abdomen revealed coarse and plaque-like calcification originally interpreted as being compatible with carcinomatosis secondary to ovarian carcinoma (Fig. 2). Death resulted from a transfusion reaction during treatment for the accompanying severe anemia. Autopsy revealed numerous large lipoid granulomas, without evidence of malignancy. These probably resulted from mineral oil, at one time used by surgeons to minimize adhesions, which

Table I. Classification of pelvic extragenital tumors

	Benign	*Malignant*	*Total*
A. Congenital —pelvic kidney	4	–	4
B. Traumatic —lymphocyst	68	–	68
hematoma	2	–	2
C. Inflammatory			
I. Pelvic abscess	1	–	1
II. Appendiceal abscess	1	–	1
III. Granuloma of ileum	1	–	1
IV. Diverticulitis of sigmoid	2	–	2
V. Radiation sigmoiditis	2	–	2
VI. Lymphopathia venereum	2	–	2
VII. Oil granulomas	1	–	1
D. Neoplastic			
I. Retroperitoneal			
1. Primary			
a. Mesodermal			
Fat tumor	–	2	2
Fibrous tissue tumor	–	1	1
Reticuloendothelial system tumor (lymphoma)	–	3	3
Blood vessel tumor (hemangiopericytoma)	–	1	1
Unclassified sarcoma	–	1	1
b. Neurogenic			
i. Nerve sheath-neurilemmoma	1	–	1
ii. Sympathetic nervous system			
Neuroblastoma	–	1	1
Ganglioneuroblastoma	–	1	1
c. Embryonal—teratōma	–	1	1
2. Metastatic tumor in pelvic lymph nodes			
a. Squamous carcinoma	–	1	1
b. Melanoma	–	2	2
c. Neurofibrosarcoma	–	2	2
d. Synovial sarcoma	–	1	1
II. Urinary bladder	–	21	21
III. Gastrointestinal tract			
1. Benign			
a. Mesenteric cyst	1	–	1
2. Malignant			
a. Adenocarcinoma of sigmoid	–	2	2
b. Adenocarcinoma of rectum	–	3	3
c. Adenocarcinoma in pilonidal sinus tract	–	1	1
d. Adenocarcinoma of cecum	–	1	1
e. Melanoma of small bowel (metastatic)	–	1	1
IV. Bony pelvis			
1. Primary			
a. Chordoma	3	–	3
b. Giant cell tumor	3	2	5
c. Chondrosarcoma	–	3	3
d. Fibrosarcoma	–	1	1
2. Secondary			
a. Adenocarcinoma	–	4	4
b. Myeloma	–	1	1
Grand total	92	57	149

has been known to produce lipogranulomatosis abdominis. Review of the films following autopsy indicates the coarse plaque-like calcification is truly unlike that of ovarian carcinoma. Without the misleading history, this mistake would likely have been avoided.

Case 3. N. B. was a 59-year-old Negro woman, gravida i, para i. Progressive abdominal enlargement with 30 pounds' weight loss had occurred during the preceding year. Dyspnea, nausea, and constipation had been present 4 months. A supracervical hysterectomy had been performed 13 years before for uterine fibroids. Examination revealed a posterior pelvic tumor the size of a 28 weeks' pregnancy, thought to be ovarian in origin. However, roentgenologic examination revealed a retroperitoneal tumor obstructing the left ureter, displacing the kidney, and extending into the pelvis (Fig. 3). Displacement without invasion of the bowel had occurred. There was linear and coarse calcification in the tumor. Retroperitoneal fibrosarcoma was suggested. Retroperitoneal sarcoma, unclassified, was the diagnosis at laparotomy and subsequent autopsy.

Case 4. C. P. was a 15-year-old white girl, gravida i, para i. Four months previously she had completed at full term an uneventful pregnancy, but at the 6 weeks' checkup a 20 cm. pelvic mass was noted on the right side.

Because of the location of the tumor and the type of invasion of the underlying ilium, osteoblastic spicules on the inner aspect of the right ilium, lymphoma was the roentgen diagnosis (Fig. 4). With no other roentgenologic or physical findings, laparotomy was necessary to establish the tissue diagnosis.

Pelvic lymphomatous masses are sometimes isolated but more often are associated with generalized lymphoma.

Case 5. V. G. was a 59-year-old Negro woman, gravida i, para i. Admission complaints were dysuria and hematuria of several months' duration. There was a history of supracervical hysterectomy 9 years before and a "bladder operation" one year before. The cervical stump was attached to a mass that extended to the right pelvic wall. The patient was referred to the gynecology service for evaluation of the mass attached to the cervix. Routine intravenous urogram demonstrated the bladder tumor (Fig. 5); transurethral biopsy revealed transitional cell carcinoma of the urinary bladder.

Case 6. E. Y. was a 39-year-old white woman, gravida iv, para iii. History revealed a recent



Fig. 2



Fig. 3

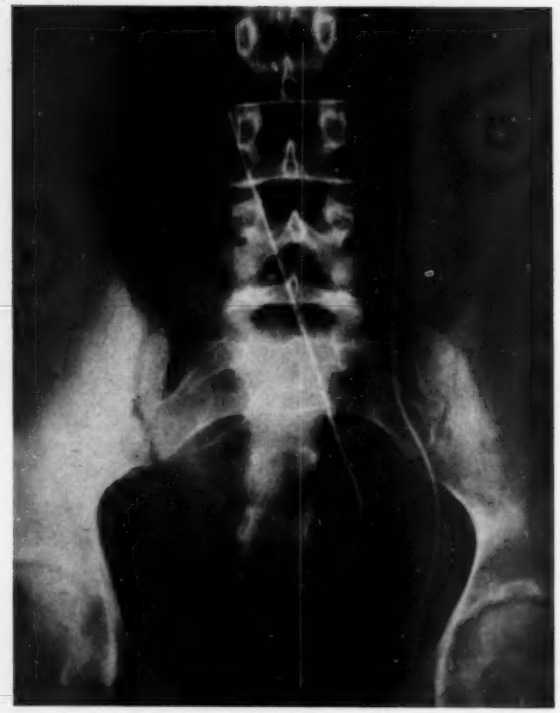


Fig. 4

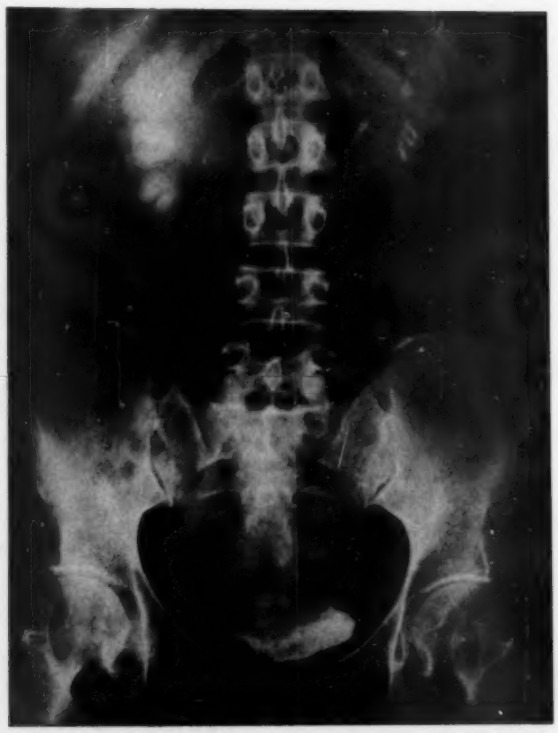


Fig. 5

bout of cramping lower abdominal pain, and the passage of bright as well as dark blood per rectum. A Stage I carcinoma of the cervix had been treated 8 months previously with radium and parametrial x-ray.

On examination a mass was felt in the left side of the pelvis; the clinical impression was recurrent tumor or a second tumor primary in the colon. Barium enema examination revealed a localized narrowing with minimal irregularity, interpreted as radiation sigmoiditis (Fig. 6). At laparotomy a 2.5 inch long mass was dissected from the sigmoid; the pathologic diagnosis was fibrosis presumably secondary to radiation.

Case 7. L. H., a 38-year-old Negro woman, gravida vi, para vi, had a history of constipation and flatulence of 4 weeks' duration. Pelvic examination revealed a clean cervix which bled profusely to touch, and a poorly defined pelvic mass. The anal canal was almost obstructed by a firm irregular perianal lesion. An accompanying pathology report of a biopsy of the lesion revealed carcinoma of the rectum. The gynecology service accepted carcinoma of the rectum as the clinical diagnosis. The patient was then scheduled for abdominoperineal resection. However, barium enema examination revealed the changes of lymphopathia venereum (Fig. 7). Since the original sections were not available for review, additional biopsy material was obtained and interpreted as consistent with that diagnosis. A subsequent Frei test was positive. There was a good response to chloramphenicol and Hegar dilators.

This case clearly illustrates, in the absence of a complete history, the necessity for (1) documentation of pathologic opinion and (2) consideration of the radiologist's opinion even though it is in the minority.

Case 8. G. M. was a 76-year-old white nullipara. Intermittent diarrhea for one year was the chief complaint. Examination revealed a tender, firm mass arising from the pelvis and almost filling the right side of the abdomen. The nature of the pelvic mass was uncertain until barium enema examination demonstrated a perforating carcinoma of the cecum with walled-off abscess (Fig. 8). One year after a right hemicolectomy, the patient was free of known disease.

Case 9. S. M. was a 59-year-old white woman, gravida i, para i, who was referred with a diagnosis of ovarian carcinoma. She complained of lower abdominal pain of six weeks' duration.

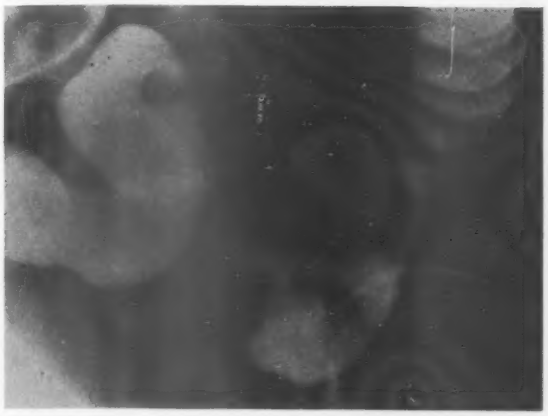


Fig. 6



Fig. 7

Examination revealed a firm, slightly irregular 12 cm. left adnexal mass indenting the anterior rectal wall. The routine intravenous urogram for pelvic mass demonstrated an indentation on the left side of the bladder and low obstruction of the large bowel (Fig. 9). A barium enema demonstrated the bowel lesion, an adenocarcinoma of the sigmoid. This was confirmed at the time of surgical resection.

Case 10. R. B. was a 35-year-old white woman, gravida iv, para iv. Nausea, vomiting, loss of appetite, and melena had been present for 3 weeks. Five years previously a malignant melanoma had been excised from the parotid area, and 18 months previously there was excision of skin and node recurrence with radical neck dissection.

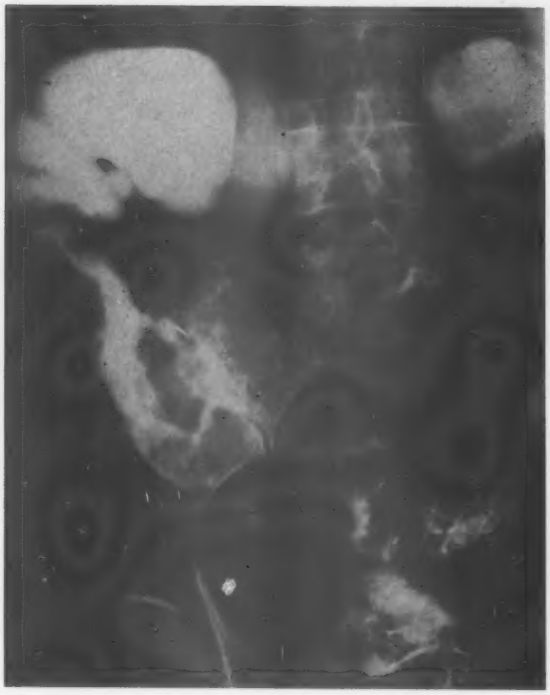


Fig. 8

Physical examination revealed a large retrovesical mass. The intravenous pyelogram showed an irregular gas-containing mass extrinsic to the urinary tract. No abnormality was found in the colon on barium enema examination. Studies of the small bowel demonstrated a large pelvic mass with central excavation communicating with the ileum (Fig. 10). The appearance of the lesion excluded diagnosis of a primary carcinoma of the small bowel. With no evidence of lymphoma elsewhere and with the history of metastatic melanoma in the neck, the radiologist's diagnosis was metastatic melanoma involving the ileum. Biopsy at the time of enteroenterostomy confirmed this opinion.

Case 11. B. F., an 18-year-old white woman, gravida ii, para 0, was referred for investigation of retroperitoneal tumor following laparotomy without biopsy "lest the peritoneum be seeded with cancer cells."

On pelvic examination a smooth mass was found high on the right side of the pelvis. The retrograde pyelogram demonstrated bilateral renal ectopia with a pelvic kidney on the right



Fig. 9

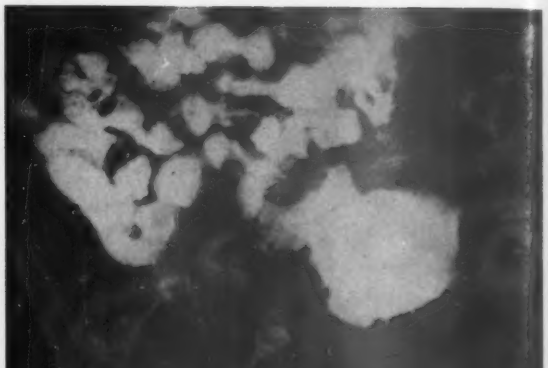


Fig. 10

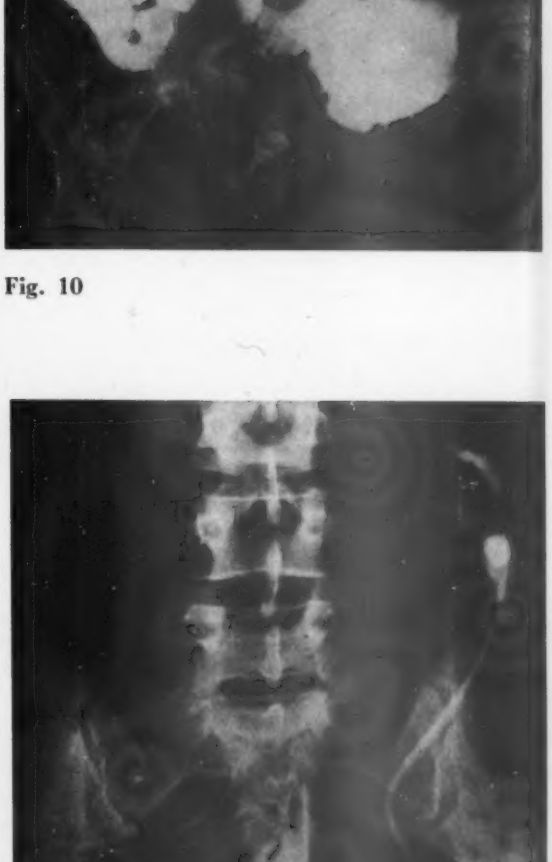


Fig. 11

(Fig. 11). Investigation revealed no further abnormality.

Case 12. V. D., a 52-year-old white gravida iii, para ii, had suffered from a profuse yellowish, watery vaginal discharge for 1 month. Uncontrolled vaginal bleeding following pelvic examination necessitated hospital admission for curettage. A diagnosis of Stage III squamous cell carcinoma of the cervix was made. Over a period of 6 weeks she received treatment by radium applications plus total pelvic irradiation. A pelvic lymphadenectomy was done 3 months later. Ten days later swelling of the right leg was noted, and pelvic lymphocyst was clinically suggested. Intravenous pyelogram confirmed this, and demonstrated right-sided hydronephrosis and hydroureter. Improvement in the renal status was demonstrated by repeat studies as the lymphocyst resolved.

Despite the severe encroachment on the pelvic veins as demonstrated at femoral venography (Fig. 12); 3 years later she was asymptomatic and apparently free of disease. An intravenous pyelogram was normal at that time.

Case 13. T. M. was a 56-year-old white woman, gravida viii, para viii, who complained of postcoital bleeding of 3 years' duration and heavy vaginal bleeding for one month. Stage III squamous cell carcinoma of the cervix with extension to the right pelvic wall was diagnosed. Irradiation was followed in 3 months by a bilateral transperitoneal pelvic lymphadenectomy. One month later there was swelling of the right leg. Two and one-half months after operation bilateral lymphocysts were palpable. The roentgenograms made at that time demonstrated soft tissue density along the pelvic walls. Bi-

lateral hydronephrosis was also demonstrated. Pelvic pneumography with nitrous oxide, shown in Fig 13, outlined the lymphocysts. Over the next few months, the edema gradually regressed and when last seen, one year after treatment, the patient was clinically free of disease, and the complicating lymphocysts had disappeared.

Case 14. C. L., a 63-year-old white woman, gravida iii, para iii, complained of weakness and fatigue of 2 years' duration. Subsequently mucoid rectal and bloody vaginal discharge had appeared. On examination there was kraurosis vulvae, leukoplakia ani, and a mass in the pelvis along the rectum with rectal ulceration. Probable diagnosis was carcinoma of the rectum. Hepatosplenomegaly and retroperitoneal mass led the radiologist to suggest leukemia as a strong possibility. Biopsies of the liver and axillary node showed malignant lymphoma "suggesting chronic lymphatic leukemia." The latter diagnosis was confirmed clinically and at postmortem examination. Death was due to diffuse hemorrhage into the gastrointestinal tract and urinary bladder. Opacification of the pelvic lymph nodes with an oily opaque medium slowly injected into the inguinal nodes showed the pelvic masses to be enlarged nodes (Fig. 14). The architecture of the nodes in lymphoma is sufficiently preserved for opacification. Squamous cell carcinoma destroys the nodes and blocks the flow of the opaque material.

Case 15. A. A. was a 56-year-old white woman, gravida v, para v, who complained of bloody vaginal discharge of 3 months' duration, progressive pain in the lower abdomen of 2 months' duration, and swelling of the legs during the preceding 2 weeks.

On pelvic examination a uterine mass was felt which involved the left parametrial area, extending to the pelvic wall and into the lower abdomen. Provisional diagnosis was Stage III carcinoma of the cervix or of the corpus uteri. Chest x-ray revealed bilateral mediastinal enlargement and bilateral small pleural effusions (Fig. 15). Lymphoma was suggested. Inguinal node biopsy confirmed this, and it was further confirmed at autopsy where it was shown that the pelvic disease was entirely retroperitoneal.

Comment

It seems evident to us that radiologic investigation of an adequate nature is of paramount importance in the diagnosis of nongenital pelvic tumors. A wide variety of pelvic masses is seen in this institution. It has been evident on repeated occasions that history and physical examination are inadequate for diagnosis and that in a high percentage of these cases radiologic evidence played a predominant role in the diagnosis. The pathologist's diagnosis is final in all cases. Cases 1 and 5 indicate how simple such investigation can often be. Particularly



Fig. 12

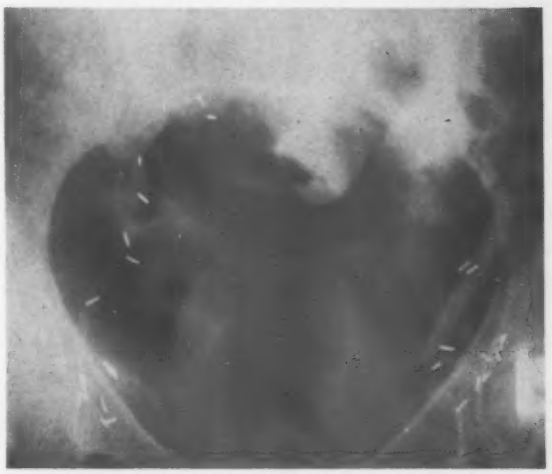


Fig. 13



Fig. 14

Fig. 15

when adequate clinical information is at hand, the surest, quickest (and therefore cheapest) radiologic route may be chosen. The intravenous pyelogram proved to be the cornerstone in such investigation and is now a routine procedure in our hands when we are confronted with these problems. It provides a gross estimate of urinary excretory function which is most helpful in treatment planning. Incidental but very valuable information regarding the gastrointestinal tract and bony structures is elicited. Also, the intravenous pyelogram is the best method of investigating abdominal and pelvic retroperitoneal structures in routine use. Retrograde lymphangiography presently under investigation at this institution shows great promise in evaluation of retroperitoneal lymph nodes. Retrograde pyelography is less safe, as these patients usually display some debility, and the possibility exists of superimposing infection on the obstructive uropathy which is usually present to a certain degree.

The films of the 15 cases presented indicate what a wealth of information, other than strictly diagnostic, accrues from radiologic consultation. The progression or regression of lesions may be assessed and metastatic involvement or other complicating factors detected. The status of the urinary and other systems may be assayed. It should be mentioned in passing that roentgen findings, especially when viewed in the light of clinical evidence, should be only rarely misleading. All of this is dependent on the fullest measure of cooperation between gynecologist and radiologist.

Summary

1. One hundred and forty-nine cases of extragenital pelvic masses in females have been reviewed.

2. Fifteen cases of unusual interest are used to illustrate the necessity and benefits of adequate radiologic investigation of these puzzling problems.

3. The necessity for the fullest cooperation between the gynecologist and his radiologic consultant is indicated.

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Extrapelvic carcinoma metastatic to the uterus

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THE uterus is not thought to be a common recipient of tumor metastases, except from adjacent organs, such as the ovary. Hertig and Gore[1] state that 4 per cent of ovarian carcinomas metastasize to the endometrium and 4 per cent of endometrial carcinomas metastasize to the ovary and note that, when both organs are involved, it may not be possible to determine the primary site. Metastatic tumors of the uterus derived from extrapelvic sources are said to be rare. In 1941, Charache[2] collected 56 published cases and added 3 of his own. The primary sites of these tumors were: breast 34, stomach 14, melanocarcinoma 2, lung 3, kidney 2. The pleura, pancreas, liver, and gall bladder each served as the primary site on one occasion. Seven additional cases have been subsequently reported (Table I) and the present report adds 8 others (Table II). Only the histories of the 5 patients whose initial symptoms suggested gynecologic disease are given in detail.

Case reports

Case 1. This 40-year-old Hawaiian woman was admitted to St. Francis Hospital on Feb. 3, 1950. She complained of bloody vaginal discharge and swelling of the abdomen. The vaginal discharge was red-brown in color and had a foul odor. The symptoms had begun one month previously. Prior to the onset of the presenting symptoms, the patient had noticed the insidious development of anorexia, fatigue, and weight loss. There were no upper abdominal symptoms. The menarche had occurred at 11 years of age. Menses, prior to this occasion, had been regular, with flow lasting 2 days. She had borne 5 children, all of whom are living and well. Physical examination revealed conspicuous abdominal distention with a demonstrable fluid wave. No masses were felt. Pelvic examination revealed the uterus to be fixed and the pelvic floor to have a hard, rigid consistency. The external cervix had a hemorrhagic granular appearance. Histologic examination of a cervical biopsy revealed the covering and glandular epithelial cells of the cervix to be uniform, mature mucous columnar in type. The epithelial basement membranes were intact. The supporting stroma, however, was filled with pleomorphic, mucus-secreting epithelial cells of the signet-ring type. They were arranged in cords and showed little tendency toward gland formation (Fig. 1). This was interpreted as an adenocarcinoma, probably of gastric origin. Cytologic examination of the peritoneal fluid revealed the presence of neoplastic cells. Gastrointestinal x-ray studies revealed a definite deformity of the distal half of the stomach, which had the appearance of a malignant neoplasm. The patient was placed on custodial care and died approximately 6 weeks later. Unfortunately, a necropsy was not obtained.

Case 2. This 42-year-old woman of Portuguese origin was admitted to St. Francis Hospital on Jan. 7, 1959, with the complaint of abdominal pain. This was intensified after eating. The symptoms had begun one month previously and had gradually increased in intensity. The menarche had occurred at 12 years of age. The menses had been regular with a 28 day cycle. She had experienced mild uterine cramps at the time of menstruation since 1942. She had borne two children, both now living and well. Physical examination at this time failed to reveal any significant findings. An excretory urogram and cholecystogram were negative. Roentgen examination of the gastrointestinal tract revealed slight coarsening of the mucosa of the greater curvature of the stomach, suggestive of gastritis. No tumor or

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Table I

Author	*Year of publication*	*Age*	*Primary tumor*	*Site, uterine metastases*	*Symptoms*	*Ovarian involvement*
Williams[3]	1945	32	Stomach	Cervix	Postprandial nausea, weight loss	?
Ratner[4]	1948	65	Right kidney	Endometrium	Hematuria and vaginal bleeding	0
Oota[5]	1950	43	Stomach	Cervix	Hemorrhagic vaginal discharge, epigastric pain	Bilateral
Oota[5]	1950	35	Leukemic, chloromyelomatous sarcomatosis	Cervix and endometrium	Hemorrhagic vaginal discharge	Bilateral
Boysen[6]	1951	65	Pancreas	Cervix	Vaginal bleeding, weight loss, anorexia, nausea	Bilateral
Cruz[7]	1954	47	Breast	Cervix	Hematuria, dysuria, menorrhagia	?
Gresham[8]	1956	66	Pancreas	Endometrium	Foul, hemorrhagic vaginal discharge	0

Table II

Case No.	*Race*	*Age*	*Primary tumor*	*Site, uterine metastases*	*Symptoms*	*Ovaries or peritoneum involvea*	*Remarks*
1	Hawaiian	40	Stomach	Cervix	Foul, hemorrhagic vaginal discharge	?	See case summary
2	Caucasian	42	Stomach	Endometrium	Periodic vaginal spotting	Bilateral	See case summary
3	Japanese	34	Stomach	Endometrium	Vaginal spotting	Bilateral	See case summary
4	Japanese	45	Appendix	Endometrium	Menorrhagia	Right	See case summary
5	Japanese	39	Stomach	Cervix and endometrium	Vaginal hemorrhage, abdominal swelling	Bilateral	See case summary
6	Japanese	57	Stomach	Cervix	Epigastric pain, constipation, difficulty in urinating	Bilateral	Original diagnosis by perineal biopsy. Necropsy case
7	Korean	20	Stomach	Cervix	Epigastric pain, lymphedema, lower extremities	Bilateral	Necropsy diagnosis
8	Japanese	24	Stomach	Cervix	Epigastric distress, weight loss, ascites	Bilateral	Necropsy diagnosis

ulcer was noted. The patient was discharged without specific treatment 3 days after admission. She was readmitted on March 16, 1959, with the complaint of vaginal spotting associated with greatly intensified uterine cramps at the time of menstruation. Pelvic examination revealed an enlarged uterus with palpable adnexa. There were no other significant physical findings. Rotengen examination now revealed a wide-mouthed diverticulum high on the lesser curvature of the stomach. There was no gastric ulceration or mass although the mucosal pattern was coarsened and prominent, suggesting gastritis. A laparotomy was performed on the sixth hospital day. Each ovary was enlarged to double the normal size, was white, lobulated, and had a solid consistency. The uterus was enlarged. The posterior wall of the gastric cardia was fixed to the posterior peritoneum. The mucosa in this area showed marked ulceration. There was gross tumor involvement of the peritoneum, omentum, and splenic hilum. A supracervical hysterectomy and bilateral oophorectomy was performed. There was no gross abnormality of the endometrium or myometrium. Histologic examination revealed a metastatic, signet-ring type of neoplasm within the uterine lymphatic channels and endometrial stroma (Fig. 2).

Cells of this type were also seen in the ovaries, Fallopian tubes and omentum. The patient died 3 months after operation.

Case 3. This 34-year-old Japanese woman was admitted to the Kapiolani Hospital on Feb. 26, 1959, with the complaint of spotting in the middle of her previous menstrual cycle. There had never been any menorrhagia, metrorrhagia, or cyclic irregularity. There was a mild, non-irritating leukorrhea. She had noted a mass in the lower abdomen one week previously. There were no urinary symptoms. She had had moderate nausea for 2 weeks. Pelvic examination revealed a 15 cm. mobile, rounded midline mass in the region of the uterus, which was considered to be a uterine myoma. A laparotomy was performed on Feb. 27, 1959. The stomach was conspicuously thickened and filled with carcinoma, so that the distal half of the organ had a "leather bottle" appearance. The omentum was stiffened and studded with white nodules measuring 2 to 3 mm. in diameter. The right ovary measured 15 cm. in diameter and had a knobby outer surface. The left ovary measured approximately 3 cm. in diameter and had an irregularly lobulated outer surface. The uterus was grossly normal. A palliative subtotal hysterectomy and bilateral salpingo-oophorectomy was performed. Histologic examination of both ovaries revealed the normal, structural elements to be replaced by mucus-secreting, signet-ring cells. Sections of the uterus showed the myometrium to be free of tumor. The endometrium contained tiny clusters of tumor cells, both within the stroma and within the lymphatic channels (Fig. 3). The ovarian and endometrial adenocarcinoma was considered to be metastatic from the stomach tumor. This patient died 4 months after this procedure.

Case 4. This 45-year-old Japanese woman was admitted to Kuakini Hospital on July 25, 1960, with the complaint of vague lower abdominal discomfort which had begun one month previously. Two weeks after the appearance of these symptoms, she developed an extremely heavy menstrual flow. She consulted her gynecologist who noted a firm mass fixed to the right side of the uterus. This resembled a uterine myoma. He elicted the information that she had had an operation 5 years previously consisting of resection of the terminal ileum, appendix, cecum, and ascending colon for carincoma involving the appendix and cecum. There was no evidence of local or distant spread at the time of operation.

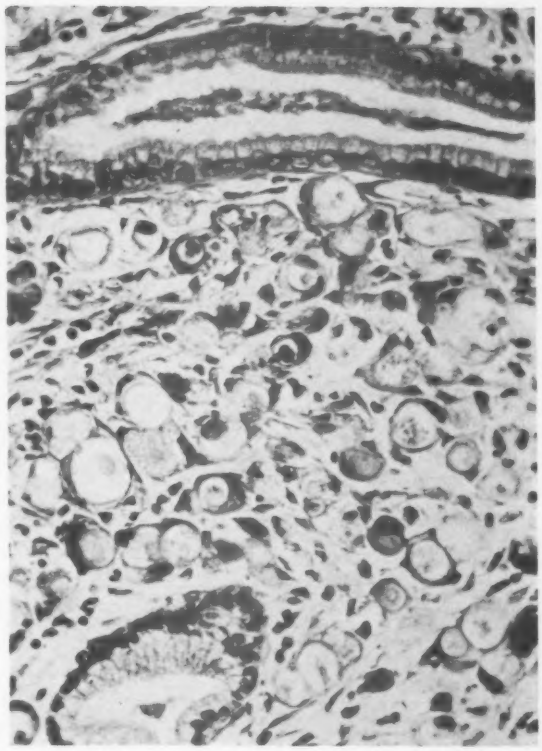


Fig. 1. Case 1. Section of endocervix showing signet-ring cells (metastatic gastric carcinoma) in stroma, with normal endocervical glands.

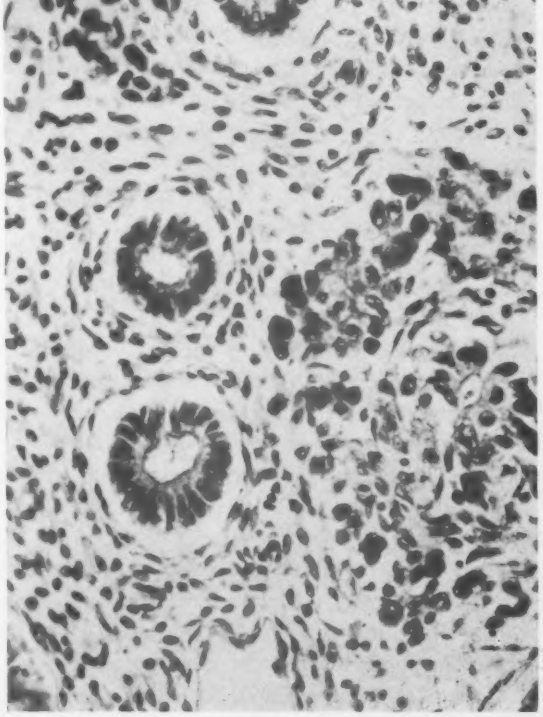


Fig. 2. Case 2. Section of endometrium showing clusters of metastatic tumor cells (gastric origin) in stroma.



Fig. 3. Case 3. Section of endometrium showing plug of metastatic tumor cells (gastric origin) in stromal lymphatic channel.

Recently, she had coughed up a small amount of blood-tinged sputum. A curettage was performed. Histologically, in the endometrium, there were sheets of tall, mucus-producing columnar cells which were similar to those noted in the intestinal mass removed 5 years previously (Fig. 4). This was interpreted as metastatic adenocarcinoma, derived from the appendix. The uninvolved endometrium itself was normal. The endocervix was free of tumor. Chest x-ray revealed a 7 cm. round mass in the left posterior gutter. A laparotomy revealed induration of the pelvic organs and right parametrium. A palliative hysterectomy and oophorectomy was performed. Gross inspection of the specimen revealed a continuous mass extending from the right ovary and broad ligament to the right lateral aspects of the uterus. On section, this was found to penetrate the entire thickness of the uterine wall and reach to the endometrial surface. The patient was still alive one month following this procedure.

Case 5. This 39-year-old Japanese woman was admitted to the Queen's Hospital on Nov. 2, 1952, with the complaint of abdominal swelling of 3 weeks' duration and vaginal bleeding. The latter required 2 pads per day and had started 2 weeks previously. Her last normal menstrual period had been in September. The menarche had occurred at 14 years of age; she had 28 day cycles with flow ordinarily lasting 5 to 6 days. There had never been any dysmenorrhea. She had 7 children, all alive and well, with the last delivery having occurred 4 years before this illness. Physical examination revealed the abdomen to be enlarged and there was a fluid wave. The external genitals were normal. There was fresh bleeding from the vaginal vault. The crevix was firm and the adnexa were difficult to palpate. A cervical biopsy showed the stromal tissue to contain sheets of mucus-producing, signet-ring type cells. This was interpreted as a Grade IV adenocarcinoma, probably of gastric origin (Fig. 5). A laparotomy was performed on the day after admission. The peritoneal cavity contained 4 L. of ascitic fluid. The distal portion of the stomach had a hard, rigid consistency. The peritoneum was covered by a thick cake of whitish-gray tissue. Biopsies of the peritoneum revealed tumor tissue similar to that seen in the cervix. The patient died on Nov. 26, 1952. At necropsy, a 4 cm. ulcer was found on the mucosa of the distal pylorus. Its base was formed by mucus-producing, neoplastic epithelial cells similar to those noted in the cervix. The autopsy disclosed that the endometrium, as well as the cervix, was involved by the tumor.

The three additional patients noted in Table II were found to have clinically unsuspected metastases at necropsy. In each case there was a definite primary adenocarcinoma of the stomach.

Comment

It is not possible to judge the exact frequency of metastatic tumor of the uterus since there are too few cases for statistical analysis. The 8 patients noted in this report were seen in 4 hospitals from 1950 to 1960. This number exceeds those reported by other authors from 1941 until the present, suggesting that the paucity of reports stems from a lack of interest, rather than a lack of cases. It seems likely, however, that the racial pattern of Honolulu may have favored the appearance of more of these tumors than has been encountered elsewhere. It has

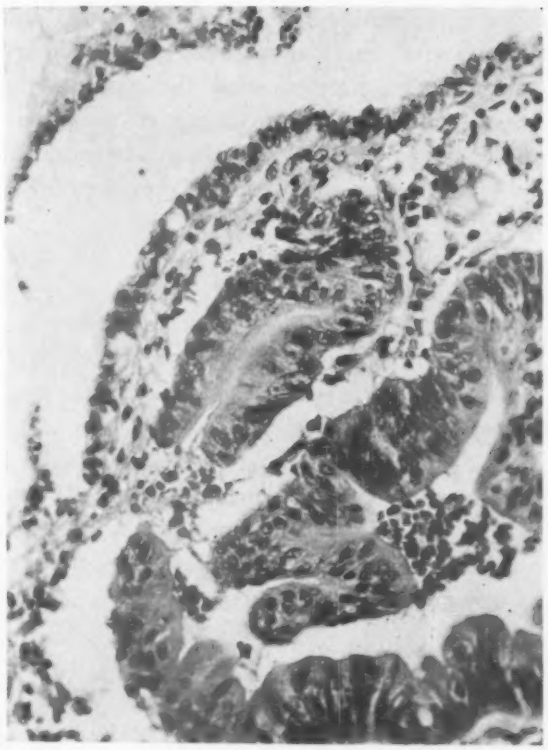


Fig. 4. Case 4. Section of endometrium showing sheets of metastatic mucous-columnar cells (appendiceal carcinoma) in contrast with normal endometrium.

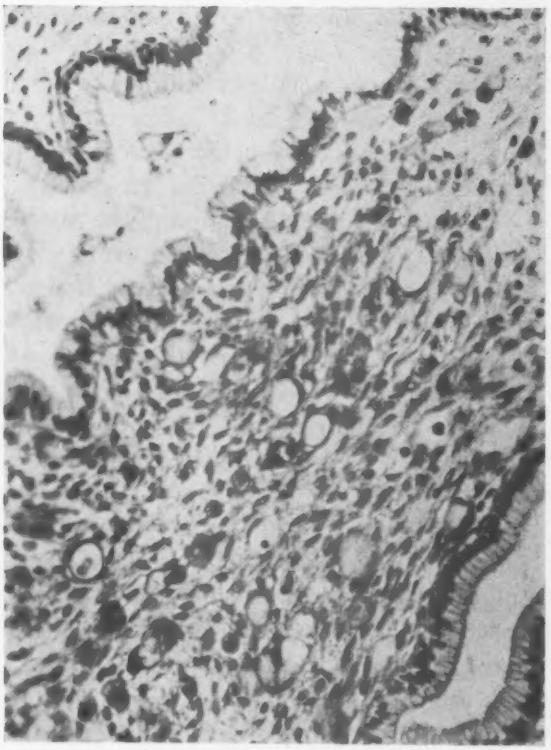


Fig. 5. Case 5. Section of endocervix showing signet-ring cells (metastatic gastric carcinoma) in supporting stroma, with normal endocervical glands.

been shown by Quisenberry and co-workers[9] that there is a high incidence of gastric cancer among Japanese, and these people now constitute approximately 35 per cent of the local population (estimate for 1958, Office of Health Statistics, Hawaii State Health Department). Four Japanese women with gastric cancer are included in this report.

One of the most striking features of this study is the youth of the victims. Eleven of the 15 cases noted in Tables I and II are below the age of 50 and 8 of these had gastric cancer. Tamura and Curtiss[10] have shown that gastric cancer in young adults is predominantly a disease of women. Twenty of their 28 cases occurred in women below 35 years of age, and all of their cases in patients below the age of 30 were in women. This contrasted sharply with their figures for all age groups, which showed that the males constituted two thirds of the cases (166 of 251). It is probable the combination of this factor with the high incidence of gastric cancer in the Japanese accounts for the large number of our cases and the preponderance of stomach tumors among them.

Most of the patients had ovarian and pelvic peritoneal metastases as well as uterine involvement. It is likely that, in most cases, these precede those in the uterus, which is invaded by way of lymphatic channels. When the ovaries are not involved, the uterine tumor is probably the result of hematogenous spread. The association of abnormal uterine bleeding with ovarian enlargement always raises the suspicion that a tumor is present, which involves both organs. When this combination occurs during the childbearing period, the likelihood that this tumor is derived from an extrapelvic source is not so remote as published reports would indicate and, if the patient is Japanese, there is a very real danger that she has a gastric cancer.

Ovarian involvement was noted in over half of the young women mentioned in the

report by Tamura and Curtiss, and 2 of these patients (Cases 7 and 8 of this series) were derived from their collection. They felt that their findings supported Willis'[11] contention that "the functionally active ovary is more prone to metastases than is the senile ovary." The almost exclusive limitation of the uterine metastases to the childbearing period gives further support to this opinion. It suggests that both the origin and spread of gastric cancer are subject to hormonal influence. All of the gastric tumors in this group of patients fall into Mulligan and Rember's[12] "mucous cell carcinoma" classification, which they thought showed a significant onset before the age of 40. On the other hand, their "intestinal cell carcinoma" was not represented in this series, in spite of the greater tendency of this tumor to occur in women. They found that this tumor type usually arose after the age of 40.

In cases of mammary carcinoma reported by Cruz,[7] of renal carcinoma seen by Ratner and Schneiderman,[4] and of appendiceal carcinoma in this series (Case 4) vaginal bleeding developed 4 years, 6 months, and 5 years after surgical removal of the primary tumors. This suggests that the gynecologist should suspect the possibility of secondary malignancy when this symptom occurs in an individual who has had a previous operation for cancer.

Summary

1. Eight cases of metastatic carcinoma involving the uterus are reported, of which 7 were primary in the stomach and one was derived from the appendix.

2. Five of the patients sought medical care because their presenting symptoms were due to the uterine involvement.

3. The factors which favor this pattern of metastasis are discussed.

I wish to acknowledge the assistance of the following hospitals and pathologists in collecting these cases: St. Francis Hospital, Dr. R. Chappell; Kapiolani Maternity Hospital, Dr. C. Curtiss; Queen's Hospital, Drs. P. Tamura and H. Civin.

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Extragenital metastases to the uterus

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THE pattern of early metastatic progression from many sites of primary malignancy is relatively well established. However, when this extension has involved the vascular system, the further localization of tumor emboli is often bizarre.

The presence of metastatic carcinomatous breast tissue in an encapsulated leiomyoma of the uterus seemed to be one of these unusual instances. A recent case with these findings stimulated our interest in this subject. Reference to the literature confirmed our impression regarding the rarity of our case since but 6 cases[14, 18, 26, 33, 35, 45] of extragenital neoplasms with metastases to a leiomyoma have been reported. We found also that, although spread to the uterus from adjacent pelvic organs, particularly the ovaries, is frequently seen, metastatic carcinoma localized in any part of the uterus from extrapelvic organs is relatively uncommon. To date, some 150 cases are recorded with the breast and stomach as the most common primary sources. This probably does not represent the total incidence of this condition for relatively few large necropsy series on specific malignancies are available which list all the sites of metastases encountered. The apparent rarity of our case and the fortuitous circumstances involved in its discovery prompted this report.

Case report

M. W. was a 39-year-old white woman, para 3-0-2-2, referred to us by the radiologist supervising her postoperative x-ray therapy for therapeutic castration. Fourteen months prior to admission, the patient had a radical mastectomy performed for a scirrhous adenocarcinoma of the breast. A study of the pathologic condition revealed 3 involved axillary nodes. Following operation and primary healing, she was given x-ray therapy totaling 4,200 r to the axilla and supraclavicular area and 3,880 r to the internal mammary chain. Several months prior to admission, she complained of pain in the right scapular area and also in the posterior sacral region. X-ray examination revealed a metastatic lesion of the sacrum. The blood alkaline phosphatase level at that time was 17.2 Bodansky units (normal, 2.5 to 4.0). Further local radiotherapy to the sacrum was given. It was felt that the disease had progressed to a stage when a shower of osseous metastases could be anticipated and that castration was indicated without delay.

Physical examination of the patient disclosed a well-developed, somewhat thin woman who complained of pain in the sacral area. There was no evidence of local skin recurrence in the surgical scar. The left axilla was indurated and the overlying skin was immobile. The contralateral breast and axilla were free of masses. No signs of pulmonary disease were elicited and no organs were noted on abdominal palpation. Pelvic examination revealed a parous introitus, well-epithelized cervix, slight enlargement of the uterus, and no adnexal masses.

Laboratory studies showed: hemoglobin level 13.9 Gm.; white blood cells 7,200 per cubic millimeter with a normal differential count; urinalysis negative; sedimentation rate 32 mm. in 45 minutes; alkaline phosphatase 14.0 Bodansky units; inorganic phosphates 3.0 mg. per cent; calcium 10.9 mg. per cent; nonprotein nitrogen 37 mg. per cent. X-ray survey revealed a metastatic lesion of the sacrum but no further evidence of spread.

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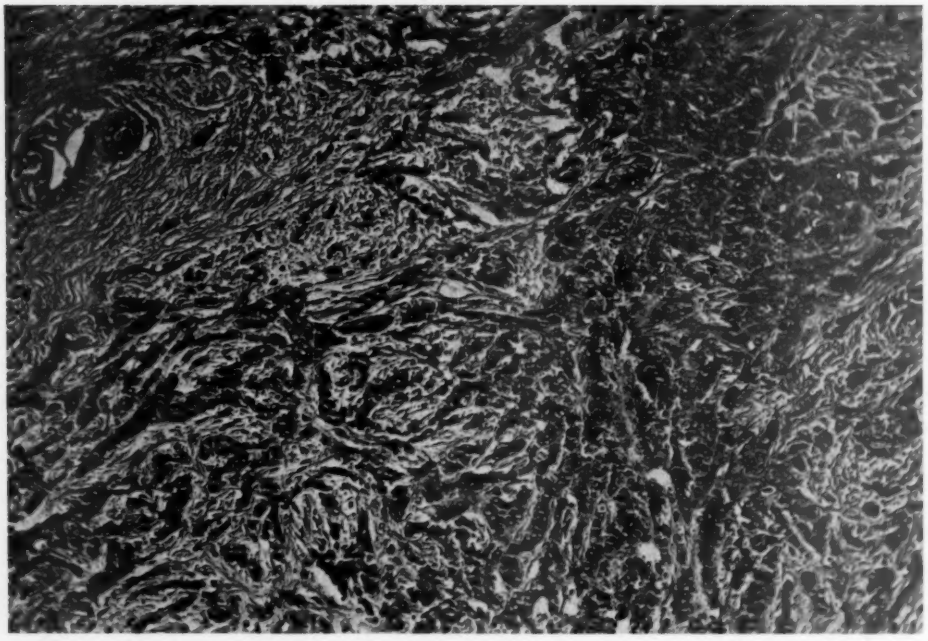


Fig. 1. Photomicrograph of the primary breast adenocarcinoma. The lesion is moderately well differentiated and contains the interlacing fibrous areas typical of the scirrhous type. (Hematoxylin and eosin. ×100; reduced ⅙.)

At laparotomy the uterus was found to be enlarged to the size of an 8 weeks' pregnancy with a posterior wall myoma measuring 5 by 5 cm. The ovaries appeared normal. The liver was free of nodules. Bilateral oophorectomy and supracervical hysterectomy were performed.

Pathologic examination of the specimen disclosed a uterus measuring 7 by 8.5 by 5 cm., distorted in its transverse diameter by an intramural myoma in the posterior wall. Although having a characteristic gross appearance, sections of the myoma showed that it contained a poorly differentiated adenocarcinoma of scirrhous nature with all the appearance of breast as the site of origin. The lesion was within the center of the myoma and had relatively abrupt borders with the adjacent muscle tissue. Neither ovary showed evident metastases, and tumor emboli were not noted in the broad ligament or tubal lymphatics or venules. The endometrium was velvety and was not remarkable on microscopic examination.

The patient had a benign immediate postoperative course but died of the disease 14 months after discharge.

Comment

Once viable tumor tissue has entered the vascular system, any chance impingement within a near or distant organ is at least theoretically possible. Tumor emboli disseminated in the systemic arterial blood stream must be distributed to the different viscera in proportion to their relative blood supplies. We might expect that metastatic tumor due to dissemination by this route would appear most frequently in richly vascular tissues. This does not appear to be true of such tissues as skeletal muscle or spleen. Within the pelvis, the ovaries are commonly the site of early distant metastases, e.g., Krukenberg's tumor. The adjacent uterus, with its extensive vascular supply, should be as susceptible to this random spread as any organ. This would not seem to be so if a generalization is to be made based upon the paucity of such cases in the literature. Probably this is partially the result of incomplete reporting of the findings at autopsy studies. However, it does seem that myometrial involvement, in the absence of ovarian spread, is probably quite rare. Turksoy[41] reviewed the incidence of metastatic breast carcinoma in the ovaries removed at castration and at autopsy. Thirty and 42 per cent of the ovaries, respectively, in her material, were involved. No case of

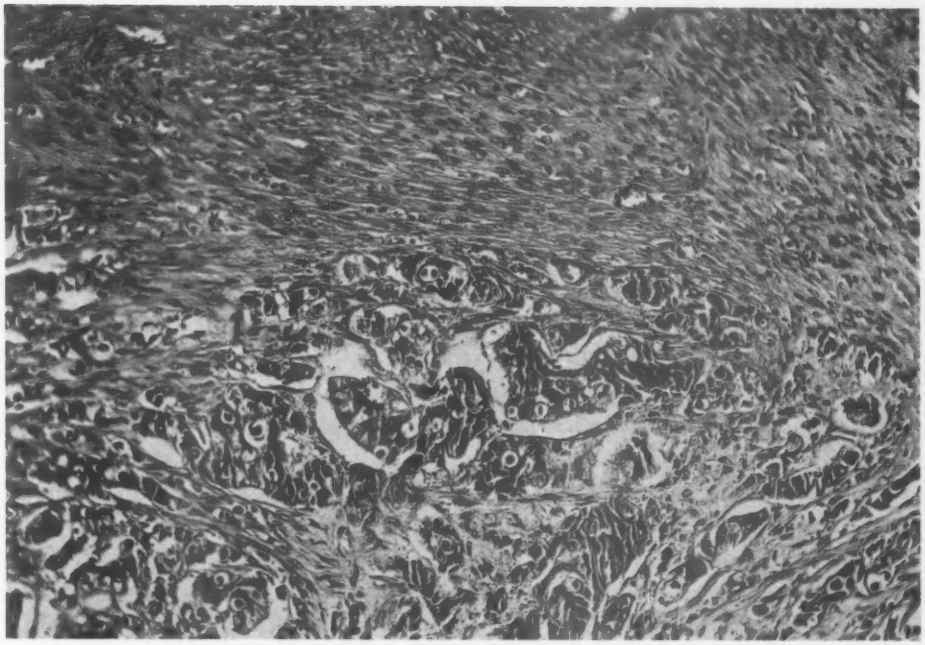


Fig. 2. The metastatic lesion within the leiomyoma. The scirrhous nature of the implant is seen and the rather abrupt junction of the tumor and muscle tissue is demonstrated. (Hematoxylin and eosin. ×100; reduced ⅙.)

uterine spread was noted although ovarian involvement was usually bilateral.

What factors exist to explain this unusual pattern of tumor spread in closely adjacent organs? Much of the work on the problem has been teleologic rather than experimental. Virchow[42] felt that organs which are frequently the site of primary tumors are seldom affected by metastatic growths. The uterus is certainly high on the list of organs affected by primary cancer. However, the lung is similarly a common primary site and equally prominent as a receptor of tumor emboli.

As mentioned earlier, the uterus seems to be readily susceptible to local metastases which occur by direct invasion from its peritoneal surface or by way of lymphatics. The primary lesions are usually other pelvic organs (ovaries, tubes, bladder, or rectum) or occasionally located caudad in the body. Local metastases can also result from implantation on the endometrium of fragments of tubal or ovarian carcinoma spread intraluminally. These appear to occur in about 10 per cent of these growths although at times it is difficult to exclude a lymphatic mode of extension.[27, 29, 31] The other means of spread to the uterus is by blood-borne tumor emboli. Recent studies have clearly indicated that neoplastic cytemia, as evidenced by examination of random blood specimens, is quite common, particularly in advanced stages of malignancy. There may be several reasons why the uterus is less commonly involved by these tumor emboli. One of the earliest explanations for this selectivity phenomenon was the relationship of the main arterial stem of a particular organ to its immediate cephalad trunk. When this junction approached a right angle, many of the tumor cells would be swept by the ostium of this vessel to more distant organs. The hypogastric artery in its origin from the common iliac has some tendency to fit these criteria. A second reason for the rarity of secondary uterine tumors may be related to the nature of the organ as a muscular mass. Metastatic growths are rare in all muscular organs whether skeletal, cardiac, or smooth. Earlier authors theorized that this was because of the movements of these structures, the supposition being that this hindered the effective lodgment of blood-borne emboli. Neither of these explanations seems particularly logical.

We may again refer to the lung as a constantly mobile organ which nevertheless harbors metastatic growth. Recent work on this perplexing question points toward some individual tissue factor, such as metabolic rate, oxygen tension, or pH, which governs its frequency as a site for tumor spread. Willis[44] has summarized this subject well in stating that "particular tissues provide optimal chemical or metabolic conditions for the growth of particular tumours; different tumours have different optimal requirements and therefore each tumour has its own preferential sites of metastases."

He further shows that, in the case of paired organs, the metastases frequently affect both members of the pair. Metastases in a single tissue usually occur as multiple nodules. This indicates that a tumor which has proved itself capable of colonizing a particular receptive host tissue is more than likely to establish multiple colonies in that tissue or in both members of a pair. Ovaries, for example, have been reported to be more alakaline than most body tissues, whereas the uterus may have a low pH because of lactic acid produced by its high muscle content. These are merely suggestions of differences in uterine and ovarian metabolism to explain the disparity in the incidence of metastatic growths. To quote Willis again, it is apparent that "different seeds require different soil."

Extragenital metastases to the uterus were reviewed by Charache.[6] He collected 56 cases, more than 50 per cent arising in the breast. Additional reviewing enabled us to collect 102, 7, 11, 12, 16, 19, 20, 22, 23, 43 earlier cases and since then some 94 further cases have been reported.[1, 3, 4, 6, 9, 17, 30, 32, 34] Primary sites, in order of frequency, have been: breast, stomach, colon, rectum, kidney, ureter, and lung. Isolated cases arising in the pleura, pancreas, bone, liver, and gall bladder are recorded. Two melanomas are included.

The first reported case of blood-borne metastases to the uterus from an extragenital site appears to be that of Legg.[22] The primary tumor was a melanoma of the eye.

When metastases to the uterus do occur, these growths are situated in the endometrium more often than in the muscle. No apparent explanation exists for this fact, which again suggests tissue susceptibility differences.

Metzger,[23] Walter,[43] and others have reported further selectivity once the tumor has invaded the muscle wall. They describe several instances of extensive invasion of the myometrium by metastatic tumor which surrounded existing myomas but did not invade them.

Thus the core of an encapsulated neoplasm such as the leiomyoma found in our case seems to be an unlikely place for a tumor embolus to lodge. However, this area is not particularly resistant as a milieu for neoplastic metabolism. Sarcomatous transformation, generally central in location, occurs in 0.41 to 2.02 per cent of the cases of leiomyoma reported.[25] The lower figure is corroborated by the number of unexpected sarcomas found in such tumors removed during myomectomy. Three recent series[10, 13, 21] represent an aggregate of 2,114 leiomyomas of which 0.52 per cent were sarcomas. These are malignancies developing in tissue normally present in the uterine wall but we also know that ectopic glandular tissue in the myometrium has been shown to be capable of neoplastic growth. The development of adenocarcinoma in an adenomyotic focus is an example of this phenomenon. Colman and Rosenthal[8] graphically demonstrated the progression toward malignancy of glandular endometrial tissue within the myometrium. A second glandular lesion of this type is the benign adenomatoid tumor of the myometrium which has been occasionally described.[5] Superficially they may be mistaken for an adenocarcinoma (this type of lesion was considered in our case) although the cells of the ductlike structures are uniform in appearance and the growth is usually in continuity with the serosa.

In the 6 cases of extragenital malignancy metastatic to a leiomyoma previously reported, the primary tumor was in the lung in one,[33] in the stomach in 2,[18, 35] and in the breast in 3.[14, 26, 45] As previously noted,

these latter organs are the two most common sources of tumor emboli resulting in general uterine metastases. One of the breast cases[26] is of particular interest in that the leiomyoma was removed 2 years after mastectomy for adenocarcinoma of the breast. Subsequently, vaginal and cutaneous metastases have been noted although the patient is alive 8 years after the original operation.

Whether the tumor found in tissue study in our case became implanted within a preexisting myoma or, through some local factor, caused an overgrowth of surrounding myometrial tissue resulting in a myomatous lesion must remain speculative. The latter theory seems to be less likely.

The circumstances involved in the discovery of this lesion evoked discussion as to the procedure of choice at the time of surgical castration. It is not our intent to evaluate the present indications for this mode of therapy of breast carcinoma or the ideal time for castration procedures. A brief perusal of the literature on this subject leaves one with the impression that the problem is unsettled at the present time. At one extreme, castration, through surgical approach, is advocated as an integral part of the primary treatment to be performed with the mastectomy for its prophylactic value.[36] The opposite approach is also suggested in which oophorectomy is relegated to late palliation with adrenalectomy.[15, 40] The gynecologist is more directly faced with the decision as to the type of ablation procedure to be elected.

Simple bilateral oophorectomy will leave the patient with a functionless and potentially dangerous uterus. For this reason, our usual tendency, in cases where the oophorectomy is performed for bilateral ovarian disease, whether inflammatory or neoplastic, would be to perform simultaneous total hysterectomy. In these castration procedures associated with breast carcinomas, we must compromise between this inclination toward "complete" pelvic operation and an attempt to minimize the surgical morbidity and mortality in a patient afflicted with a possibly fatal disease. This decision must be based upon evaluation of each individual case but some data are available which are thought provoking.

We do know that the myometrium and endometrium are responsive to hormonal stimulation as is breast tissue. If there is an aberration in end-organ response in the development of a mammary neoplasm, a so-called estrogen dependency, might not this be the case in the uterine end organ of the same patient? Although we can present no concrete figures in this regard, several authors[24, 25, 27, 39] have noted an interesting association between mammary tumors and uterine cancer, particularly carcinoma of the corpus. Twenty-five cases of coexisting tumors are recorded. Taylor[38] compiled 10 cases of primary uterine malignancy associated with breast carcinomas in a study of the latter group. These represent 55 per cent of the cases of multiple tumors in this series from Memorial Hospital. We believe that this figure is of significance as was the close proximity of time relationship in the development of the breast and uterine growths which averaged 1 year, 4 months. Incidentally mentioned are 2 cases which may have been metastases to the uterus but no details were given.

We do not advance these few cases as statistical material suggesting concomitant extirpation of the uterus in patients with breast carcinoma. However, it is our feeling that superacervical hysterectomy can be accomplished without materially increasing the risk to the patient. This would certainly seem to be indicated when the castration procedure is performed early in course of a breast carcinoma as a prophylactic procedure. It should also be considered in those cases where metastases are limited to the axilla. When the operation is relegated to palliation for widespread osseous involvement, there is admittedly room for discussion as to the proper gynecologic approach.

Conclusions

1. A case of adenocarcinoma of the breast metastatic to the core of a uterine leiomyoma is presented. Six similar cases are noted.

2. A review of the literature disclosed that

metastases to any part of the uterus from extragenital primary malignancies are uncommon.

3. The explanation for this remains obscure. The selectivity phenomenon of metastatic growths would seem to be related to an interplay between tumor embolus and host tissue metabolic factors.

4. Because of the fortuitous discovery of the uterine lesion in our case, the addition of hysterectomy at the time of therapeutic or palliative surgical castration is considered.

We wish to express our gratitude to Dr. Leon Motyloff, pathologist of the Woman's Hospital, New York City, for reviewing the histologic material and for submitting a case report from his records.

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Detection of gynecologic cancer by fluorescence microscopy

A simple, rapid method suitable for mass screening

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THE early detection of gynecologic cancer may be based upon pathologic or histochemical findings. The techniques of Papanicolaou and his co-workers[12] are time-consuming and their universal application is limited by the prolonged training required to learn the characteristic nuclear changes. There has been a recent reactivation of research in the cytochemical field to find methods of differentiation between normal and abnormal cells. This investigation is centering around the nucleic acids and their formation and identification through the use of organic dyes, fluorescent in nature, with laboratory equipment using ultraviolet light, isotope tracers, and the electron microscope.

The origin and distribution of cellular nucleic acids has been the target of an enormous amount of research. Investigators have postulated and set up working formulas. These theories of development attempt to evaluate the ergastoplasm. Desoxyribonucleic acid is thought to consist of phosphates, desoxyribose sugar, purines, adenine, guanine, and two pyrimidines, cytosine and thymine. Rearrangement of these in the cell results in different kinds of desoxyribonucleic acid (DNA) specific to a given species. A substance called ribonucleic acid (RNA) is also found. It is thought that this product is derived from the DNA and is said to differ in that thymine is absent and uracil takes its place.

A simple cell consists of a membrane enclosing a substance called cytoplasm. Within this material there is found a nucleus also with a limiting membrane and one or more nucleoli. The cell as a whole contains water, proteins, organic acid, inorganic minerals, etc. This amazing complex apparatus or system is revealed under the electron microscope. Research workers are just beginning to fathom all the intricate network.

There are two nucleic acids found in nature.[6] Thus it follows that there are two nucleoproteins. The acids are desoxyribonucleic acid, designated DNA, and ribonucleic acid, designated RNA. DNA is found in the chromosome area of the nucleus and is bound up in some way with the formation of the genes. It is thought that DNA is the progenitor and extrudes RNA into the cytoplasm of the cell.

The nucleic acids are connected with protein synthesis, growth, and carcinogenesis. DNA is found as a constant.[6] It is the same in each species and its tissues. It also has been noted that in cancer cells certain changes take place in the cytoplasm before nuclear changes take place, namely, RNA appears as granules. If this primary change in carcinogenesis is noted here, the DNA of the nucleus may not be affected until the cancer is far advanced. The endoplasmic reticulum under the electron microscope appears as canals radiating from the nucleus. Thus, if

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DNA elaborates RNA and this combines with protein substances, the appearance may be of regularly spaced granular particles that may be designated as basophilic granules. When the reticulum holding the granules is seemingly poorly developed, it appears to connote malignant tendency.[13, 14]

Pathology teaches that a growth of similar cells, for example epithelial cells, and tissues is the same throughout the body. It is modified only by needs for differentiation in a given viscus. In gynecology the germinal epithelial cell is rarely seen under the microscope. The basal cell contains the highest DNA and RNA content. As the cell is extruded to the surface, these substances disappear until the dead desquamated epithelial cell shows none.

In contradistinction, in cancer cells there is an increase in RNA of the cytoplasm of the cell. In addition, there is an enlargement of the nucleus and its DNA content. These divergent characteristics could form the basis of a test for cancer if a suitable dye and proper illumination were devised.[10, 11]

Fluorescence microscopy appears to be the best avenue of investigation. The fluoresceins[9-11] have been extensively used. Most of the methods were either time-consuming or otherwise complicated. The primary objective was to develop a staining procedure that would differentiate the two nucleic acids. The fluorochrome, acridine orange, was used by many investigators because of its histochemical affinity for these acids.[5, 7, 15]

The practical application to differentiate the two acids was emphasized by von Bertalanffy and is designated the AO, or Bertalanffy, test for cancer detection.[1-3, 13, 14]

Material

Clinical material from my office laboratory forms the basis of this report.[4, 16, 17] The test to be of value must be simple, rapid, and suitable for mass screening. The cost must be minimal, and the ordinary basic laboratory equipment found in the average doctor's office must be used. The only additional investment was the light source, filters, and the staining materials.

Primary obstetric-gynecologic smears were made on each first office visit of 1,523 patients. Yearly examination appointments were made. Patients with atypical cases not due to inflammation, trichomonas, or monilia were re-examined at 3, 6, or 9 month intervals. Patients with atypical smears suggestive of malignancy were hospitalized and Papanicolaou smears and biopsies done.

Colored photomicrographs, 2 by 2, were made of all types of normal cells, thus establishing a norm. Thereafter pictures were taken of all atypical cells suggestive of malignancy. Normal smears were discarded. All atypical smears were filed.

Method

The ordinary standard microscope with a 1.25 Abbe condenser was used. A BG 12 (Schott) filter, 2 mm., accentuates the ultraviolet range of light. A protective filter, Wratten G 15 for the eyepiece completes the microscopic attachments. The light source was an HBO 220 watt ultraviolet light in a high-pressure burner housing. A transformer makes the setup practical for the ordinary AC current.

The principle of the lighting technique is as follows[8]: Fluorescence is the property of emitting invisible radiations and visible light as a result of the absorption radiation. Visible violet or blue light may serve as an exciting source. The blue light source range, 350 to 450 microns is least destructive to living organisms and permits longer periods of examination. Two filter combinations are needed to isolate radiation of the desired wave length for excitation and to provide a dark background free from ultraviolet radiationation. A primary filter, violet-blue, or violet, is placed in the course of the light before it strikes the silver mirror. Unwanted visible light is thus removed from the illumination. A secondary filter absorbs radiation passed by the primary filter and at the same time transmits new visible fluorescent light transmitted by the specimen (smear). The secondary filter (Wratten G, etc.) is placed in the ocular. The two filters together are called the cross filter technic.

This combination is good for routine screening and color photomicrography.

A Leica camera "back" was used with a unit for photomicrographs. The light source was a Carl Zeiss ultraviolet lamp. The microscope was a Bausch & Lomb. This variation of equipment indicates the adaptability of items that happen to be in the laboratory. For the research worker more elaborate outfits are available from the optical companies.

Smears were collected with the use of the well-known speculum (no lubricant), cotton swab, and spatula scraping techniques. Smears were fixed immediately in equal parts of 95 per cent ethyl or isopropyl alcohol and diethyl ether. Fixation for at least 15 minutes is desirable. Longer periods of time, even a day or two, do not seem to affect staining qualities. After removal from the fixative, the slides may be stored in a suitable container and stained at leisure. Vital staining may be done on an egg albumin prepared slide but must be stained at once, scanned, and discarded.

Fixation of the cellular material dehydrates it. Water must be put back (rehydration) into the cell before it is stained. This is done by dipping the slide successively for 10 dips each in solutions of 80, 70, and 50 per cent alcohol; washing for 10 dips in distilled water; dipping for 6 seconds in 1 per cent acetic acid to dissolve out the hemoglobin of the red cells; washing again for 10 dips in distilled water; then staining in 0.01 per cent acridine orange solution for 1 to 3 minutes. A stock solution of 0.1 per cent acridine orange in distilled water is used with a phosphate buffer M/15, pH 6.0, as a vehicle. A final 1 to 4 minute dip in the phosphate buffer removes excess dye. To differentiate the nuclei and nucleoli, calcium chloride M/10 is used ½ to 1 minute.

A 22 by 40 mm. cover glass, mounted with a few drops of buffer, is used to prepare the slide for scanning. Excess solution is absorbed by blotting paper. Slides are then examined under the fluorescence microscope.

After scanning, slides may be destained by removing the cover glass in distilled water and placing the slides in 50 per cent isopropyl alcohol for 2 to 5 minutes. This permits restaining and comparative evaluation by Papanicolaou, hematoxylin-eosin, silver nitrate, etc.

Evaluation of smears

By means of the AO technique, the following cells were detected in cervicovaginal smears:

Cornified cells: cytoplasm green; nucleus white pyknotic.

Precornified cells: cytoplasm green or grayish green; nucleus is larger and more vesicular—whitish green.

Parabasal cells: outer and inner vary in degree in cytoplasmic color from dull red-brown to more red color. The nuclei are larger than the precornified and are yellow-white. Occasional red nucleoli are seen.

Basal cells: the diameter of the entire cell varies in size from 12 to 20 μ and the nucleus takes up 7 to 12 μ of this space. The cytoplasm is orange-red and the nucleus is yellow.

Endocervical cells: the cytoplasm is lacelike in structure. When visualized in "picket fence" strands, the columnar cells show the cytoplasm orange-red with yellow nuclei and at times red nucleoli.

Leukocytes: the cell wall is rarely visualized. The nucleus appears white-green, segmented, and irregular in shape.

Lymphocytes and monocytes: have a faint gray cytoplasm.

Red blood cells: do not stain; if present, appear as a faint round green-black shadow.

Histiocytes: characterized by a bean-shaped nucleus. The cytoplasm is lacelike and faint red-gray. The nucleus is yellow.

Mucus: appears as pale green threads or a shadowy gray-green film.

Bacteria: show characteristic shape and stain a brilliant red.

Trichomonas vaginalis: a flagellate organism—stains red with a yellow gutlike area (so-called nucleus).

Monilia: shows an orange-red mycelia with interspersed spores of the same color. This coloring makes for rapid diagnosis.

In senility the nucleus often appears hypo-

chromatic, the cytoplasm being a pale gray-green with a faint tinge of red.

Hormonal readings with nuclear index can be done routinely.

Comment

The object of this paper is to evaluate the practicability of the AO test. No attempt is made to give detailed observations on atypical and malignant changes. The most common type variations observed are emphasized.

Atypical cornified squamous cells: show red granules around the nucleus.

Atypical endocervical cells: show orange-red cytoplasm with large yellow nuclei and two or more orange-red nucleoli.

Pregnancy cells: cytoplasm is orange-red; nuclei, single or multiple, yellow; nucleoli, multiple, light red color.

Malignant cells: under low power stand out as a beacon light in contrast to normal cells. These special cell areas under high power reveal first the red fluorescence and second malignant morphologic changes in the nucleus; a green color in the chromosome area at the nuclear periphery; nucleoli are orange-red. Criteria such as irregular nuclear membrane, multinucleation and giantism, altered ratio of nucleus to cytoplasm, and other nuclear malignant changes aid in diagnosis.

Clinical cases were classified as follows: Class I, negative; Class II, atypical, due to inflammation, pregnancy, etc.; Class III, suggestive of malignancy; Class IV, with cytologic criteria of malignancy.

Table I

Age	*Class I*	*Class II*	*Class III*	*Class IV*
10-19	31	1		
20-30	316	17		
31-40	402	27	3	1
41-50	422	39	5	
51-60	142	23	5	1
61-70	73	5	1	2
71-80	4		2	
81-90	1			
	1391	112	16*	4†

*Seven Class III, biopsy showed carcinoma; 2 Class III, biopsy showed metaplasia; 4 Class III, biopsy negative; 3 Class III, no biopsy.

†Four Class IV, confirmed by biopsy.

Results

Table I shows the results of the cervical and vaginal smears stained by AO in 1,523 cases seen for the first time.

Summary

A simple, rapid, easily learned technique suitable for mass screening in gynecologic-obstetric exfoliative cytology has been evaluated. The normal, atypical, and malignant phases have been described. The advantage of simplicity has been emphasized. The value for mass screening has been shown.

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The screening of apparently benign cervical lesions

Cytologic examination or punch biopsy?

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WHICH is the better screening procedure, a cytologic examination or a punch biopsy, on women who have been found to have a minimal lesion of the cervix, for example, one that appears to be only a small, benign erosion? Or, should both procedures be done despite the possible added expense to the patient? Naturally, these questions are not raised when examination of the cervix so strongly suggests carcinoma that immediate biopsy is mandatory.

The most widely recommended use of cytologic procedures today is as a cancer-screening test for asymptomatic women who do not have a lesion on the cervix. The false-negative reports that at times come from all cytology laboratories suggest that cytologic examination may be inadequate as the only diagnostic procedure in the presence of a purportedly benign lesion. In the present study, we have attempted to answer the above questions by reporting on the comparisons of the accuracy of cytologic examination, punch biopsy, and a combination of these studies as cancer-screening procedures carried out on a selected group of women who had lesions of the cervix.

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This research was assisted in part by National Cancer Institute Grant No. 5688.

Method

This is a study of the 321 women with cervical lesions who were staff patients at the University of Miami–Jackson Memorial Hospital from July, 1951, through August, 1959, and who met our criteria for inclusion in the study. During this time there were approximately 34,000 cytologic studies done on patients in this department. Every woman in the study had a cervical smear and a punch biopsy performed within a month of each other; in recent years the two tests have usually been done at the same examination as we have proceeded toward our goal of obtaining biopsies of all cervical lesions immediately after making a smear.

The women in this study are not an unselected sample of patients as they are all matriculates in our Positive Cytology Registry.[1, 2] This means that to qualify all of the patients in the study had a Papanicolaou Class III, IV, or V smear at the time of their first cytologic examination or subsequently (and in this special case within 30 days of the punch biopsy). The Positive Cytology Registry was the source used for selection of the patients for this study because it made readily available a large number of patients' records which were of high quality. These contained our most complete tissue and cytology follow-up examinations. Because of this selection of patients, the findings of this report are acknowledged to be

different from those which would be expected in a sample of consecutive patients with cervical lesions coming under our care. This selective factor would increase the number of patients who had carcinoma which was found on the screening punch biopsy but should not lessen the validity of this comparison of the punch biopsy and the cytologic examination as screening tests for women who do have carcinoma.

None of the patients was pregnant at the time of the cytologic and tissue studies. White and non-white women were represented in about equal numbers. The ages were from 16 to 88 years with an average of 41 years.

A "lesion" is defined here as any departure from the normal appearance of the cervix to such a degree that the examiner recorded it as a lesion on the patient's chart at the time the punch biopsy was performed. The descriptions of the cervical lesions range all the way from "erosion" and "cervicitis" to frank "cancer." Our policy is to do a quadrantal punch biopsy with a generous sampling of any visible lesion. When there is doubt as to the limits of a lesion, tincture of iodine is applied to the cervix to locate areas that need a biopsy.

Our cancer smears are made by scraping the surface of the entire cervical orifice with a wooden spatula, reaching as far into the cervical canal as possible. A second and similar smear is made at once. In many cases more than one cytologic study was done within a month of the biopsy. Only the initial smear is used in this report because it is the important one in the evaluation of cytology as a screening procedure.

It is our practice to do a diagnostic conization of the cervix and a fractional curettage when (1) a punch biopsy shows intraepithelial carcinoma of the cervix or (2) there has been a positive report of the cytologic examination and the punch biopsy shows anything less serious than invasive carcinoma. The reasons for this policy have been explained in earlier publications from this department.[3-5] Practically all of the patients in this report who fit into the above two categories have been treated as described. For the purposes of this inquiry it satisfies the objective, which is to compare the reliability of cytologic studies and punch biopsy to group invasive carcinoma and intraepithelial carcinoma together and refer to them as a "positive biopsy" or "carcinoma."

Results

General. At the first cytologic examination (the screening smear), 253 of the 321 women in this report were found to have a positive smear, while 68 were negative (Fig. 1). The latter subsequently had a positive smear, thus becoming matriculates in the Positive Cytology Registry and participants in this study. The subsequent smears on women who originally had negative reports on cytology were made for several reasons: (1) it is our routine to make a smear on all patients admitted to the hospital, the Outpatient Department, and the Emergency Room; (2) curiosity was aroused because the punch biopsy had shown dysplasia or carcinoma; and (3) clinical suspicion of cancer was present. The screening punch biopsy of 24 of these 68 women with negative cytologic reports yielded a diagnosis of cancer, 9 with invasive carcinoma and 16 with intraepithelial carcinoma.

Eventually 210 of the 321 women qualifying for this study were proved to have either invasive or intraepithelial carcinoma. The remaining 111 women who proved not to have carcinoma nevertheless had exfoliated cells that produced a smear interpreted as positive because of dysplasia or for other reasons that are not apparent at this time. Included in these 111 women are the 67 women with positive smears and negative tissue diagnoses (Fig. 1), many of whom have not had a conization. Our experience indicates that these 67 women should all have a conization but we have not yet been able to convince every woman, especially those with no symptoms, that they should have the operation because they have a positive cytologic report. Some of these women have moved from the area and are tempo-

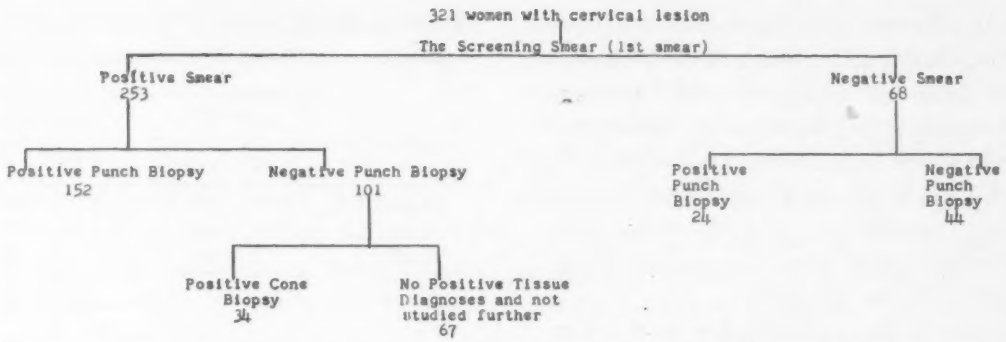


Fig. 1. The screening smears and punch biopsies on 321 women with a cervical lesion.

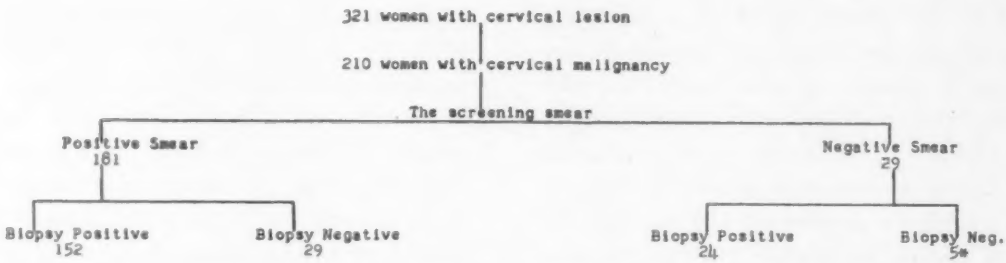


Fig. 2. The cytologic examination on 210 women with cervical malignancy. The asterisk (*) indicates the failure of both biopsy and cytology as screening procedures.

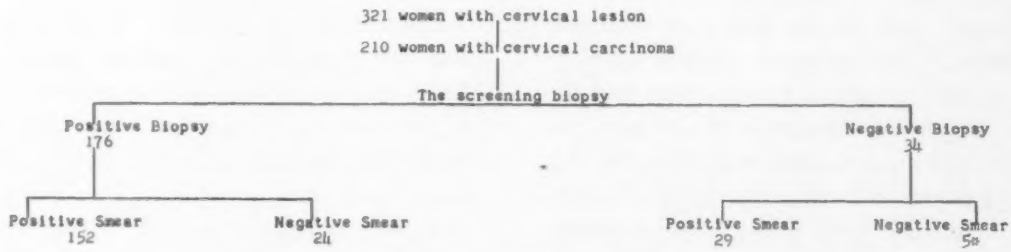


Fig. 3. The screening biopsy on 210 women with cervical carcinoma. The asterisk (*) indicates the failure of both biopsy and cytology as screening procedures.

rarily lost to follow-up. A better understanding of the unexplained positive smear is a major research objective of the Positive Cytology Registry. These women will be followed closely for a long period of time with the hope of eventually learning the meaning of this positiveness, which was often only temporary.

Of the 253 women who had a positive smear on the screening test, 152 were found to have cancer on the punch biopsy (Fig. 1). Ninety of these 152 women had invasive carcinoma and 62 had intraepithelial carcinoma.

Accuracy of the cytologic examination as a screening procedure. In estimating the comparative accuracy of (a) the cytologic examination, (b) the punch biopsy, and (c) a combination of the two as screening tests only, the 210 proved to have carcinoma need to be used (Fig. 2). One hundred and eighty-one of these 210 women had a positive cytologic report. It can be presumed that this report, if it were the only screening test done, would have led to the correct diagnosis—an accuracy of 86 per cent for cytologic examination as a screening procedure in a group of 210 women with carcinoma.

Twenty-nine (14 per cent) of the 210 women with carcinoma had a false-negative cytologic report. Carcinoma was found in

24 of the 29 women by the screening biopsy. The true diagnosis in these 29 women with negative cytologic findings would have been missed completely if a routine cervical punch biopsy had not been performed. The negative cytologic findings, obtained as the single screening procedure, would have been deceptive enough in some cases to discourage obtaining a tissue diagnosis.

Accuracy of the punch biopsy as a screening procedure. The results of the screening biopsy are represented in Fig. 3. The accuracy of the punch biopsy as a screening procedure can be determined by adding the 152 cases in which the initial smear and the screening punch biopsy were both positive to the 24 cases in which there was a negative smear but a positive punch biopsy (Figs. 3 and 2). This is a total of 176 of the 210 cases of cancer in women who could have been proved to have cancer by the punch biopsy alone—an accuracy of 84 per cent.

Accuracy of performing both cytologic examination and punch biopsy as screening procedures. The accuracy of the employment of both cytologic examination and the punch biopsy as screening procedures can be expressed by counting as failures for this plan the 5 patients (2 per cent) with carcinoma who had both a negative screening cytologic test and a negative screening biopsy (Figs. 2 and 3). This is an accuracy of 98 per cent for this combination of the two screening procedures. These 5 cases of carcinoma with negative cytologic findings and a negative punch biopsy were found because a prompt repeat of the cytologic examination had a positive result; this puzzling behavior was solved by a diagnostic conization which produced a larger specimen of the cervix in which carcinoma was found.

Comment

In Fig. 1 it can be seen that of the 253 women with a positive screening smear, 101 had a negative screening punch biopsy. Because it is our plan to further study women with positive cytologic findings and negative punch biopsies, 34 of these 101 women have had a cone specimen diagnosed as positive

Table I. Comparison of the classes of the positive smears and the final tissue diagnoses

Papanicolaou smear	*Invasive carcinoma (No. patients)*	*Intraepithelial carcinoma (No. patients)*
Class III	6	18
Class IV	29	29
Class V	56	15

—showing either intraepithelial or invasive carcinoma. The remaining 67 women, because of their positive screening cytologic tests, are naturally a source of concern to us; any one of the following applies to these 67 women: (1) there were more negative punch biopsies, (2) there was a negative cone biopsy, or (3) no further studies were done, principally because the patient disappeared or would not submit to further examinations. Some of these 67 women may have a malignant lesion and all deserve close follow-up.

Correlation of positive tissue diagnoses and the class of the positive smears. The 152 women who had both a positive screening smear and a positive screening punch biopsy are women in whom both screening procedures were successful. It is instructive to further analyze these 152 women by comparing the two tissue diagnoses that we are calling positive—intraepithelial and invasive carcinoma—with the three possible different degrees of positiveness in the smears. Table I illustrates the fallibility of dependence on the degree of positiveness in predicting the seriousness of the lesion and in measuring the urgency of learning by cone biopsy if intraepithelial carcinoma or invasive carcinoma is present. Twenty-four of the 152 women had a screening smear that was Class III, the least of our three positive classes; 6 of them had invasive carcinoma, and 18 the intraepithelial variety. It is obvious that our Class III smears are alarming enough that we will have to continue considering them "positive," contrary to the practice in some other clinics. Expectedly, in the 71 Class V smears, the most positive class, 79 per cent were obtained from women with

invasive carcinoma. The Class IV smear was equally divided between the invasive and the noninvasive types of carcinoma.

Conclusion

Under the conditions imposed by this clinical investigation, the use of both cytologic examination and punch biopsy as screening procedures for cancer of the cervix proved to be considerably more accurate than either screening procedure alone. The cytologic examination had an accuracy of 86 per cent and the punch biopsy 84 per cent; and when both tests were used, the accuracy was 98 per cent.

We wish to thank Dr. W. A. D. Anderson, Professor of Pathology, and the members of his staff for their kind cooperation.

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Evaluation of the TMK-101, "Türk," polychrome staining method in cytomorphological cancer research

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THE diagnostic value of TMK-101, "Türk," method in cancer detection was reported in a previous paper and the technique for preparing and using this new staining solution was explained.[1]

A scientific exhibit consisting of hundreds of 8 by 10 color photomicrographs and illustrations was prepared for the annual meeting of the Florida Medical Association in Miami Beach, May 2-6, 1959, and the technique and freshly stained slides were demonstrated.

The purpose of this report is to compare the cells stained by TMK-101 with the same cells stained subsequently according to the Papanicolaou staining method and to evaluate the findings.

Material and method

Scraped smears from human uterine cervices were used as material in preparing the slides. For rapid diagnostic purposes, a 4 per cent solution of TMK-101, with a 15 minute minimal staining period, was used.

For cellular morphological investigations, a 2 per cent solution of TMK-101 was prepared. A small piece of thymol crystal was added to 250 c.c. of the solution to prevent deterioration. The addition of 2 drops of one-tenth normal acetic acid to the above solution is useful for obtaining clearer and brighter coloration.

The slides were stained and mounted in exactly the same manner described previously,[1] except that a more diluted dye (2 per cent) was used; therefore, it was necessary for the slides to remain in the staining solution for a longer period of time (from 2 to 10 hours, or longer if desired, at room temperature).

The slides were then examined under the microscope and photomicrographs taken. When this study was completed, the slides were replaced in the same dye solution. After about 15 minutes' immersion, the cover slip was removed easily without manipulation. Then each specimen slide was gently removed from the staining jar with forceps and placed in fixative solution (50 c.c. ether and 50 c.c. alcohol absolute mixture). The alcohol in the fixative solution, partially, sometimes completely, removes the TMK-101 coloration. After the regular fixation time, the slides were subsequently stained according to the standard Papanicolaou method, mounted in Permount, and examined.

Thus, the same slides and cells were studied secondarily, and photomicrographs

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were taken with the same camera and printed in the same magnification.

Results

All cells and microorganisms present in the scraped smears were stained bright carmine, sky blue, or violet, and all the tones of these three colors. The detail in the nuclei, cytoplasm, and cellular membranes was stained distinctly.

Cellular membranes. The cellular membranes stained homogenously in carmine, blue, or violet. Both upper and lower membranes of a normal squamous cell had specifically fine granulation, the membrane granulation. The upper membrane also had the neighboring cells traced on surface.[5] In the presence of a mechanical cellular defect, two different torn edges belonging to two individual membranes of the cell were occasionally seen. The inner, or cytoplasmic, membrane was a shade lighter than the external, or cellular, membrane. The anaplastic or precancer cells, while having paranuclear halos,[2] showed more characteristic torn membrane edges on the outer borders.

Cytoplasm. The cytoplasm consisted of three different parts as studied with both staining techniques. One was the liquid part of the cytoplasm, second were the particles, such as mitochondria. The third part was a plexiform skeleton, seen after strong fixative effects. The first two were seen in the cells stained with TMK-101. The latter was seen as the only remaining part of the cell after fixation. Cytoplasmic globules, seen occasionally in inflammatory hyperactive cells, and fat droplets and vacuoles were observed in degenerated squamous and/or glandular cells. The coloration of the cytoplasm and particles coincided with that of the membrane. The particles assumed an intense dark coloration and were the most prominent part of the cytoplasm (Fig. 1, *A* and *B*). The fat droplets probably did not absorb any TMK-101 and thus retained a yellowish spherical shape (Fig. 1, *D*). Vacuoles were colorless, spherical or oval areas in the cytoplasm. Halos were observed frequently in the cytoplasm. Two types were studied. Each was placed in an individual category. One, the *perinuclear halo,* is a narrow and translucent area surrounding the nucleus and covered by cellular membranes on both sides (Fig. 2, *A*). The other, the *paranuclear halo,* is large and irregular in shape and one side, at least, is not covered by the cellular membrane (Fig. 2, *B*).

Nuclei. Nuclei usually stained the same color as the cell, i.e., in a red cell, the nucleus was also red; in a blue cell, the nucleus was blue; in a violet cell, the nucleus was violet, except that the nucleus was much darker.

The nuclear membrane, in normal cells, was thin and circular, sometimes oval. A well-defined, clear difference was seen between the cytoplasm, nuclear membrane, and karyoplasm (Fig. 1, *A*). In inflammatory cells, this differentiation was very poor. In fact, there was less than one shade difference between nuclear membrane and the plasmas (Fig. 1, *B* and Fig. 3, *A*). The inflammatory nucleus was swollen and appeared edematous. The karyoplasm was generally homogenous with the only prominent granulations being one or two darkly stained and well-preserved nucleoli (Fig. 3, *A*).

In anaplastic precancer or malignant cells, the nuclear membrane was, as a rule, irregularly stained, thick, and dark. In the karyoplasm there were many chromocenters of different shapes and sizes. It was frequently impossible to determine which was the nucleolus (Fig. 2, *B* and Fig. 3, *D*).

Two distinct types of malignant cells were observed. In one, the large nucleus was surrounded by a small rim of cytoplasm. In other words, the nuclear-cytoplasmic ratio was larger than in other conditions (Fig. 3, *C*). In the second instance, the nuclear-cytoplasmic ratio was not as large, the nuclear membrane was thinner, but the karyoplasm was darkened, with many chromatins (Fig. 3, *D*).

Nucleolus. The most prominent part of the karyoplasm, in normal and especially in inflammatory cells stained in TMK-101, was the nucleolus.

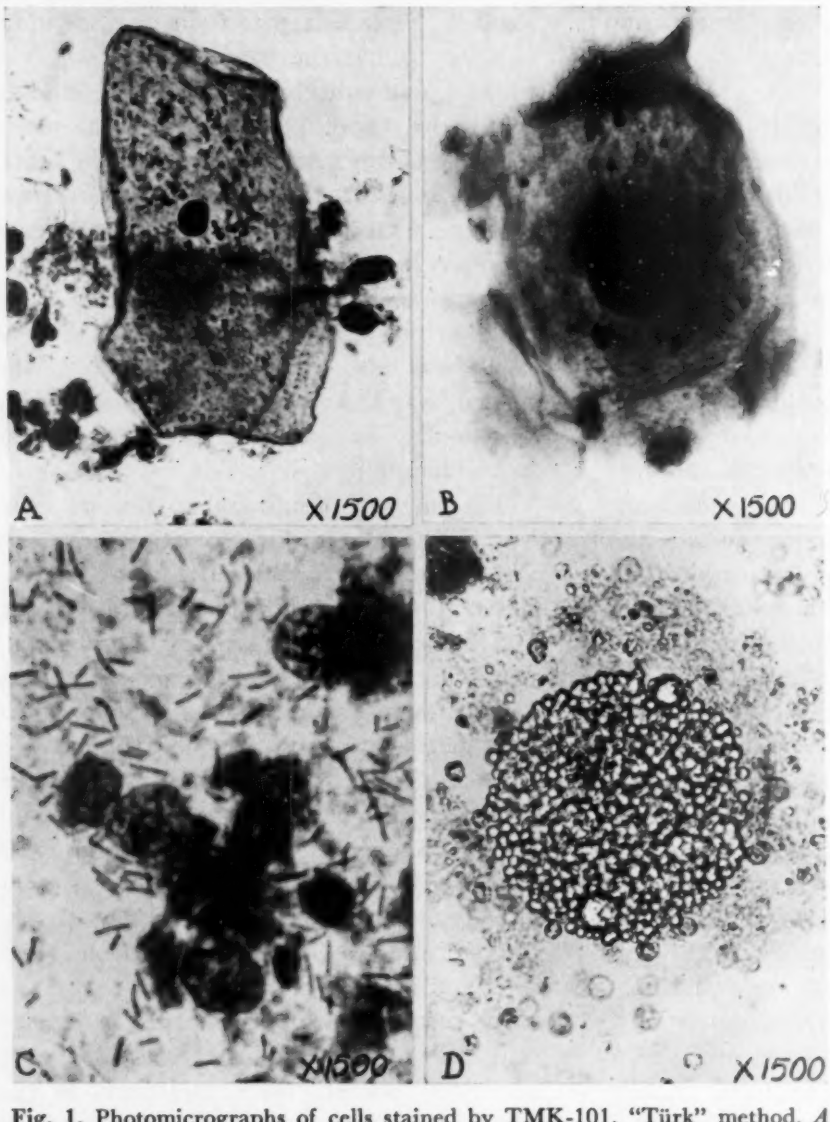


Fig. 1. Photomicrographs of cells stained by TMK-101, "Türk" method. *A,* Normal cornified cell with fine cytoplasmic and nuclear granular detail. *B,* Inflammatory precornified cell with swollen nucleus and cytoplasmic bodies. *C,* Normal vaginal smear of pregnancy showing characteristic free nuclei, Döderlein bacilli and cellular debris. (*A, B,* and *C* were taken from uterine cervical smears.) *D,* Foam cell from breast secretion smear with numerous fat particles within cell. Upon cover glass pressure, fat droplets will leave the cell, which then takes on the characteristic appearance of a foam cell stained by Papanicolaou technique.

Comment

A comparison of cells stained in TMK-101 and cells stained according to the Papanicolaou technique probably will give us a better understanding of the anatomical structure of uterine cervical cells (Fig. 4).

Fig. 4, *A* and *C* shows a cervical scraping smear stained according to the Papanicolaou technique. In an exhaustive microscopy study, it was observed that the only remaining parts of these cells were the stroma, such as the cellular membrane, cytoplasmic trabecula, nuclear membrane, and a few nuclear chromatin. The cellular fluid, cytoplasmic fine bodies, and/or mitochondria, were almost nonexistent, having disappeared during the staining process. In Fig. 4, *C* (a folded cell with paranuclear halo or the side view of a cell with a defective membrane), the nucleus is tied to the inner part of the

cell by plexiform filaments or cytoplasmic trabecula. There is no granular chromatin in this network. These photomicrographs show only the skeleton of the living cells. These results were produced by the fixatives and the dehydrating effect of the staining technique employed.

The membrane granulations were observed only by TMK-101, staining technique. Regarding these morphological findings, the cellular thicknesses were studied, measured, and compared in different pathological conditions of the cells from uterine cervices. This subject will be presented and discussed in another paper with more details reported.[5]

Cytoplasmic network or trabecula, which was clearly observed after fixation and staining (Papanicolaou method), is possibly made of contractile fibrils and the membrane granulations are most likely the membranal ends of these fibrils.

Fig. 4, *B* and *D* shows cells of a cervical smear stained in TMK-101. It is easily seen that the most prominent part of these cells is the mitochondria or globules in the cytoplasm. The nuclear membrane and chromatins are also distinctively stained. In intact cells it is difficult to see the cytoplasmic trabecula because the cellular fluid has covered the plexiform filaments. However, the fine granulations are perfectly stained, as observed under phase contrast.

Since the mitochondria or cytoplasmic granulations are very important in cellular metabolism, they may be equally important in the development of cancer. For this reason, the study of cytoplasmic granulations stained with a harmless polychrome technique, such as TMK-101, adds new findings to our present knowledge of this subject.

In Fig. 4, *E*—a hand-drawn cell picture—the morphological results obtained with two different staining techniques have been synthesized. This depiction of the structure of a stratified squamous epithelial cell closely resembles that of the natural cell.

The cytoplasm, according to these findings, may be a trabecular system that stretches out within the nuclear and cellular membranes. The seemingly thousands of vacuoles in this fine network are filled with cytoplasmic fluid and in each small opening particles known as mitochondria or cytoplasmic granulations are seen (Fig. 4, *B*). At no time did the granules change position when pressure was applied to the cover glass. Even when the cell was blown up,

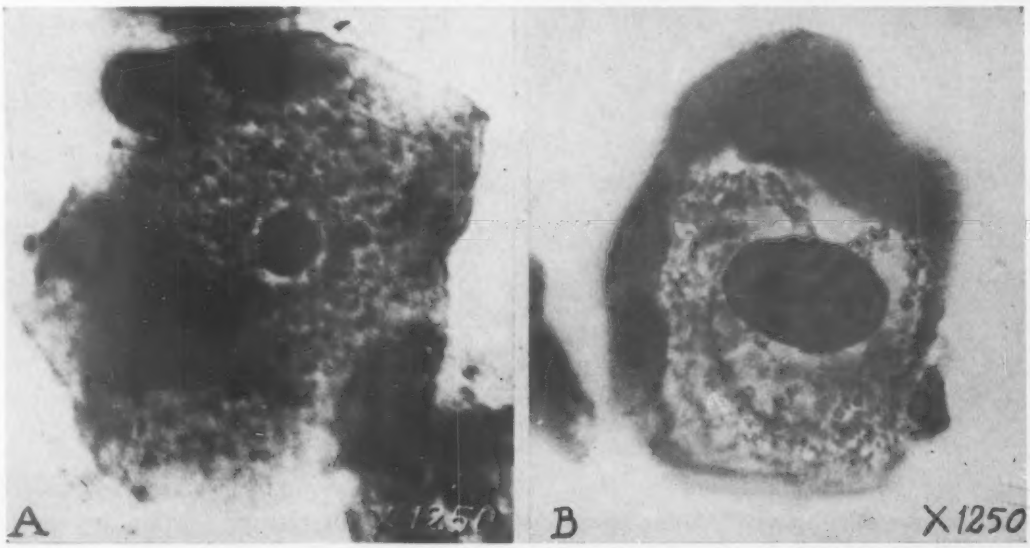


Fig. 2. *A,* Cell displaying type of "perinuclear" halo usually manifested in vaginal trichomonas infestation. *B,* Cell displaying "paranuclear" type of halo usually manifested in precancer condition of uterine cervix.

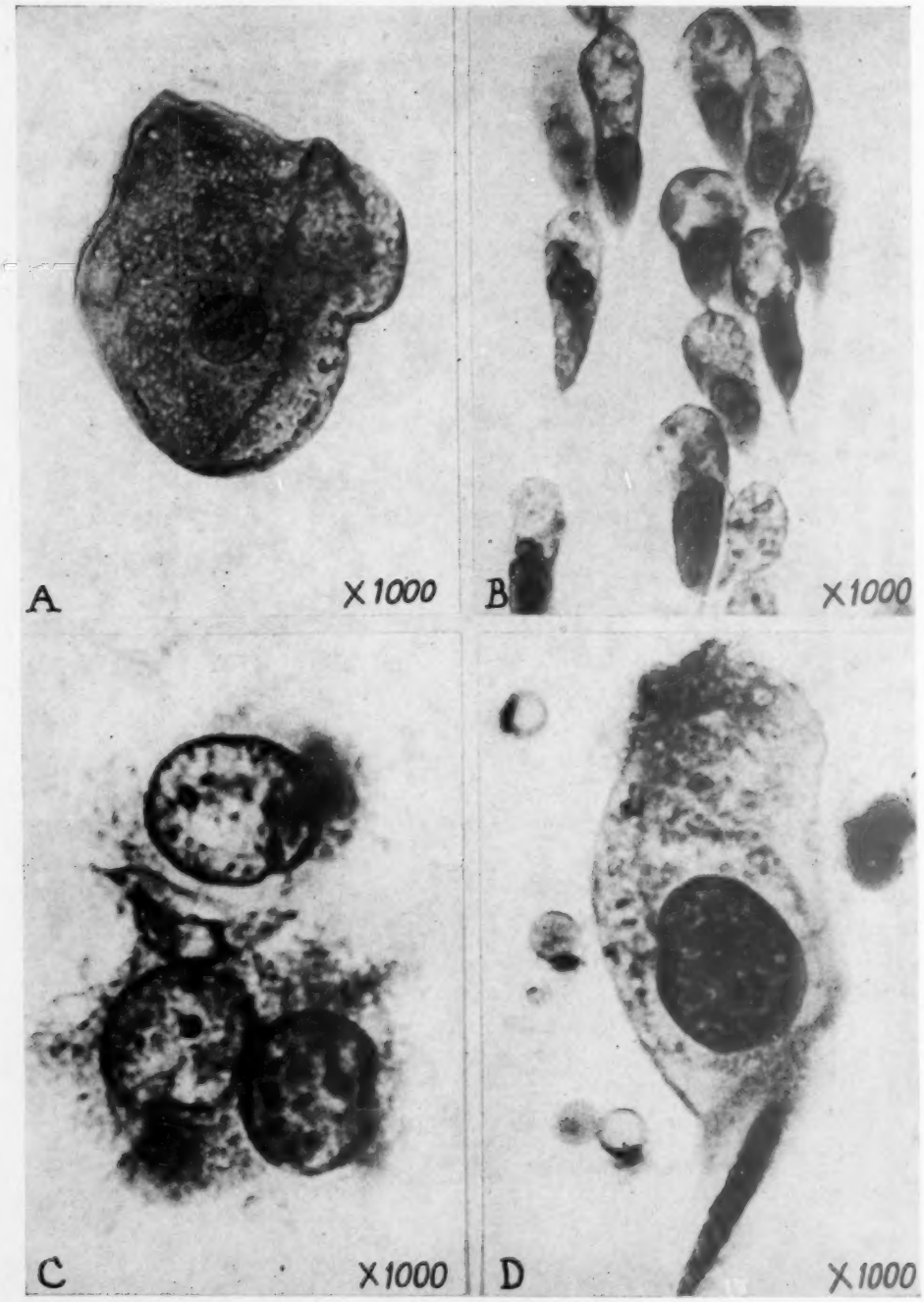


Fig. 3. Photomicrographs of cells stained by TMK-101 method. *A*, Inflammatory precornified cell with indistinct nucleus and cytoplasmic detail. *B*, Endocervical gland cells. *C*, Squamous epithelial cancer cells showing chromatin clumping at nuclear membrane, resulting in a thick and dark nuclear border. *D*, Squamous epithelial cancer cell showing chromatin clumping throughout karyoplasm with thin nuclear membrane. Erythrocytes surround the cell.

the granulations remained immobile at the periphery of ruptured area (paranuclear halos).

From this simple experiment it is evident that the granular elements of a stratified squamous cell from the uterine cervix are imprisoned within the cytoplasmic network. The same reticulum has also fixed the nucleus within the cell. The nucleus cannot move to and fro, even in the mechan-

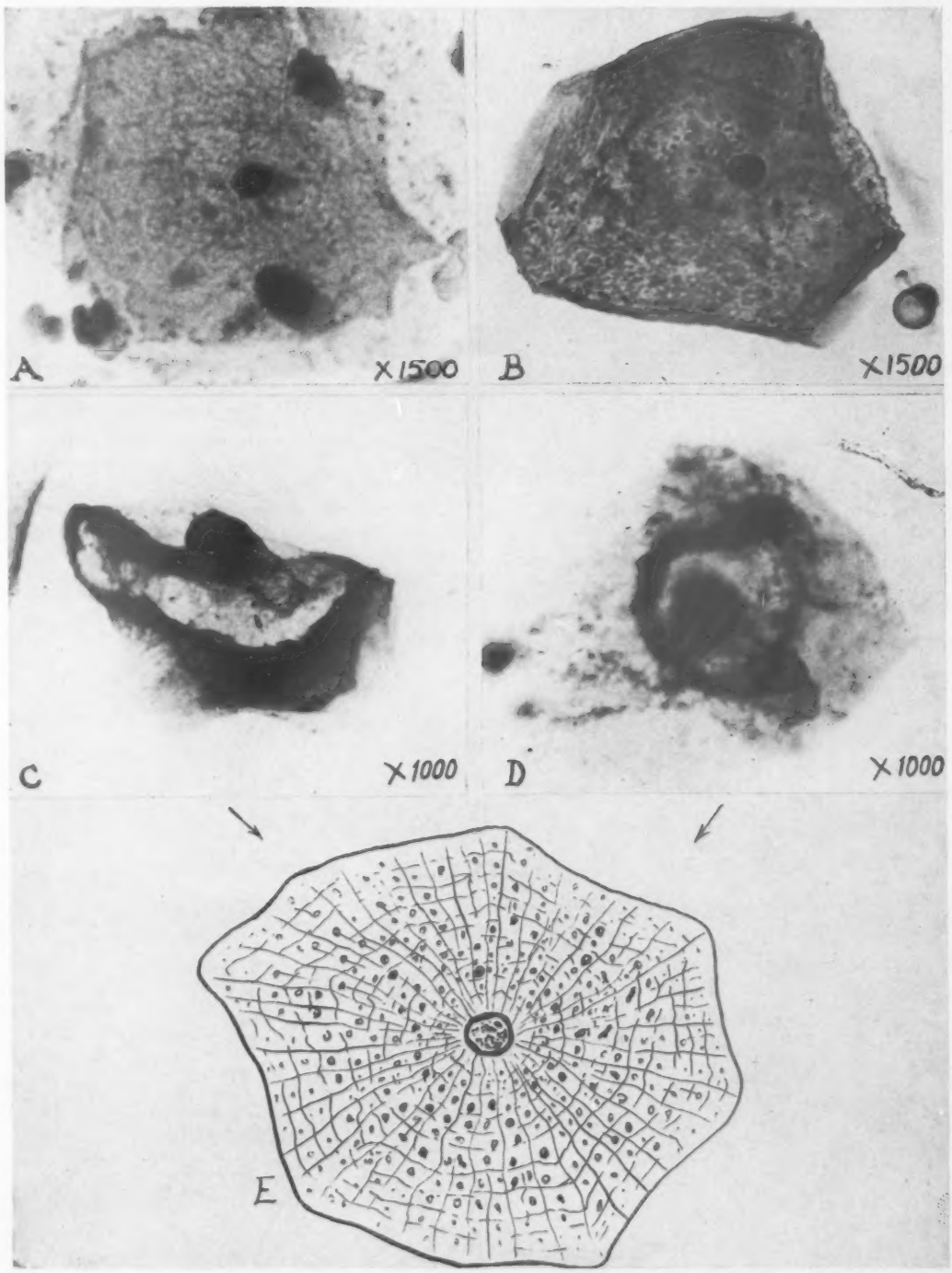


Fig. 4. *A,* Normal cornified cells stained by Papanicolaou method. Note that there is no cytoplasmic chromatin present, possibly because of the evacuated chambers. The nucleus shows no detail. *B,* Normal cornified cell from the same specimen as *A,* stained with TMK-101 method. Note there is no loss of cytoplasmic detail, and distinct chromatin is evident at nuclear membrane. Right lower corner shows an erythrocyte. *B* shows the obvious advantages in scientific research of the TMK-101 technique. *C,* Side view of a paranuclear halo cell stained by Papanicolaou technique. The nucleus seems contained within the cell by cytoplasmic filaments (plexiform skeleton). *D,* Cell with paranuclear halo showing seepage of cytoplasmic granular material through a membrane defect. Note that the cytoplasmic filaments are indistinct (TMK-101). *E,* Illustration of a stratified squamous cell construction based on observations and analysis of Papanicolaou and TMK-101 technique findings.

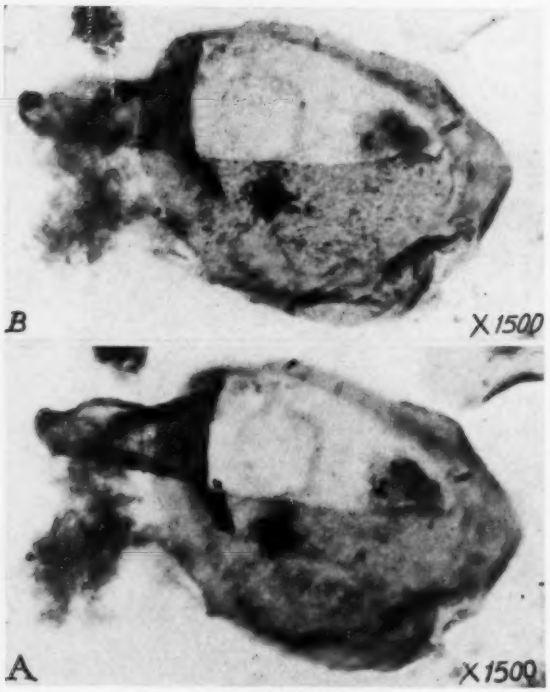


Fig. 5. *A* and *B*, Same cells stained by the TMK-101 technique, showing membranal and possible cytoplasmic defects. In *A*, focusing is set on torn membrane, leaving other cellular details indistinct and fuzzy. In *B*, focusing is on a deeper level thereby clarifying torn membrane located on cellular border and leaving torn membrane of *A* indistinct. This cellular manifestation is observed frequently in cells scraped from the uterine cervix in chronic inflammation. When torn membrane is completely freed, the resultant cell will display a paranuclear halo.

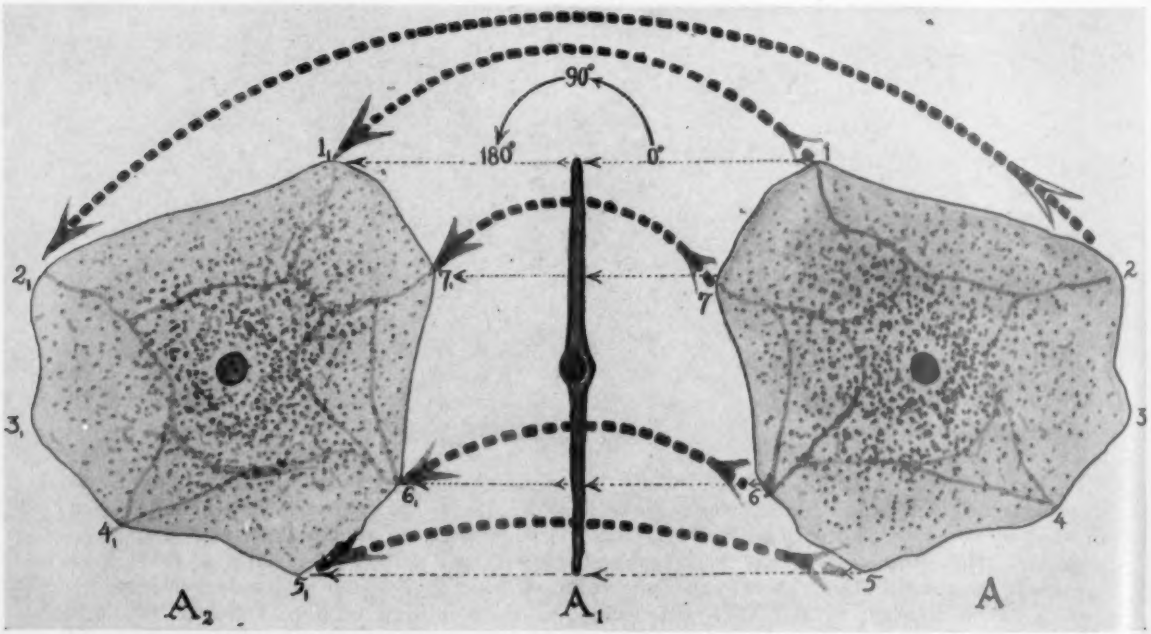


Fig. 6. Direct microscopic observation of cell thickness. The illustrated squamous epithelial cell turns through an angle of 180 degrees (A to A_2) in the mounting medium. At the 90 degree position (A_1) it is possible to observe the cellular thickness. This observation can be displayed easily by motion picture studies.

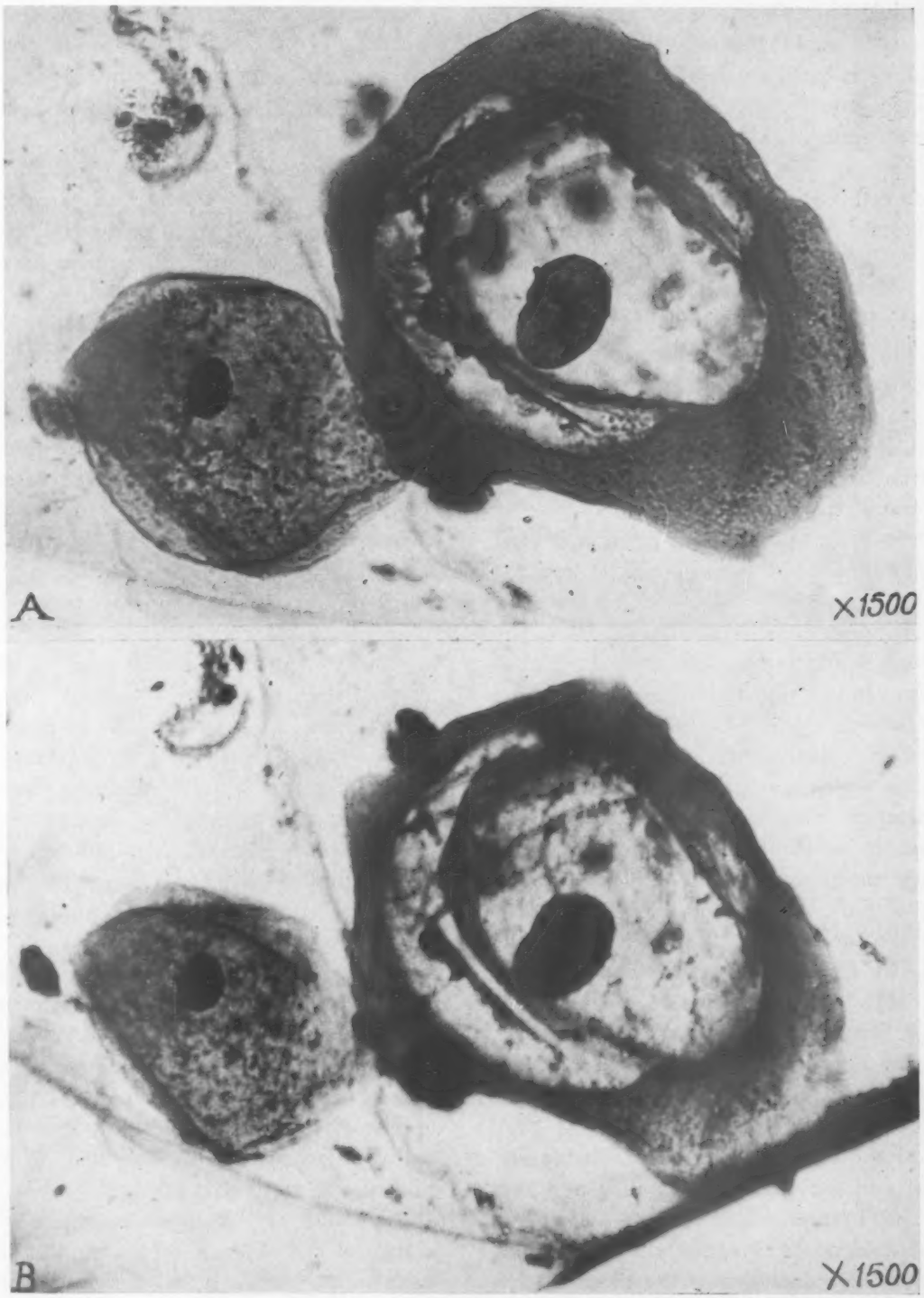


Fig. 7. *A* and *B*, The same cells under the same magnification. *A*, Cells scraped from uterine cervix and stained with TMK-101. No dehydrating agent is present with this method and the photomicrographs were taken while the cells were suspended in the mounting medium (2 per cent TMK-101; pH:3 to 4). *B*, Same cells stained by Papanicolaou technique. Note that the ether and alcohol fixative has changed the morphological dimensions of the cells and also the distribution of the chromatin. (Further information given in text.) Cells were taken from a research patient at monthly examinations by cervical scraping. She manifested clinical chronic cervicitis and cytologically a "precancer cell complex" with "paranuclear halos." The cell at right side showing superficial membrane and cytoplasmic defects is an excellent example of a paranuclear halo.

ically defected membrane and cytoplasm of the cell. In such instances, the cytoplasmic reticulum is partially broken or torn; subsequently, the nucleus is pushed away and becomes eccentric, but it rarely leaves the cell. Fig. 4, *D* shows a mechanically defected cell with a seepage consisting of cytoplasmic reticulum; granulations are seen in the cellular wound to the exterior of the cell.

TMK-101 is a water-based staining solution. The acidity of the 2 per cent solution is approximately 4. This pH is extremely close to normal vaginal acidity. For this reason, it is not likely that harmful effect on the cells or their fine structure will result from use of the stain.

Moreover, no preliminary fixation is used with the TMK-101 technique. The smeared slide is immersed in the staining solution while it is wet. After staining, the slide is mounted in the same 2 per cent TMK-101 solution. It can be and should be studied immediately. Under these conditions, cells do not lose their individual, natural fluid. There is no evidence whatever of cellular dehydration. With this technique, the dye solution is not forced into the cells. The staining mechanism of TMK-101 appears to be a diffusion phenomenon, depending upon the acidity of the individual cell. TMK-101 blue stain is a strong acid, pH 2.9. TMK-101 red stain is a weak acid, pH 6.8. Thus, a cell with a strong acidity will show an affinity for the weak acid dye and will stain red; contrarily, a weak acid or alkaline cell will absorb the strong acid dye and stain blue. Some cells probably are neutral and may absorb both blue and red dyes and become violet. There is experimental evidence supporting the belief that TMK-101 dye components are absorbed by diffusion. For example, if a slide previously stained in TMK-101 is reimmersed in a neutral fluid, such as glycerine, diluted alcohol, or an extremely diluted alkaline solution, such as 1/10,000 NaOH or 1/10,000 NH_4OH, all stained cells regurgitate their coloration and, within a short time, become colorless. In this laboratory, the same slides were restained repeatedly, followed by reabsorption. At the end of the experiment, the neutral and clear media in which the stained slides had been immersed become colored.

The point to be stressed here is that there was no change in cellular volume or shape following repeated stainings with TMK-101. The picture presented was quite similar to that seen with phase contrast.

It was not only possible, but quite practical, to study both the upper and lower surfaces or membranes of a cell merely by using the micromatic screw of a regular microscope. By use of this method, the thickness of a normal or a precancerous cell was easily measured and compared. These observations were readily obtained, particularly in the cells manifesting paranuclear halos. The halos that were produced by membranal defects were located on the upper or lower surfaces of the affected cells. If the membranal defect is located on the upper surface, the sharp edges of the defect will first become apparent to the examiner as the objective lens of the microscope travels downward, approaching the cell. The border of the membranal defect is generally the highest area of the halo cell and is similar to the cone or crater of a volcano.

As the objective moves down, the crater disappears and the nucleus and cytoplasmic granules are brought into focus. As we continue downward, the posterior membrane and its granulations are seen.

Therefore, photographs of the various cellular levels can be obtained with the microscope and camera.[5]

Fig. 5, *A* and *B* shows examples of the above. *A* manifests a torn membrane of a cell's upper surface on the initial plane. The cellular defect is seen on the secondary deeper plane and is not sharp. *B* is the same cell focused on the deeper defect plane and the initial plane, the torn membrane is diffused. By this method, it became possible to observe the cellular membranal thickness and the comparative manifestations, as well as the measurement of cell thick-

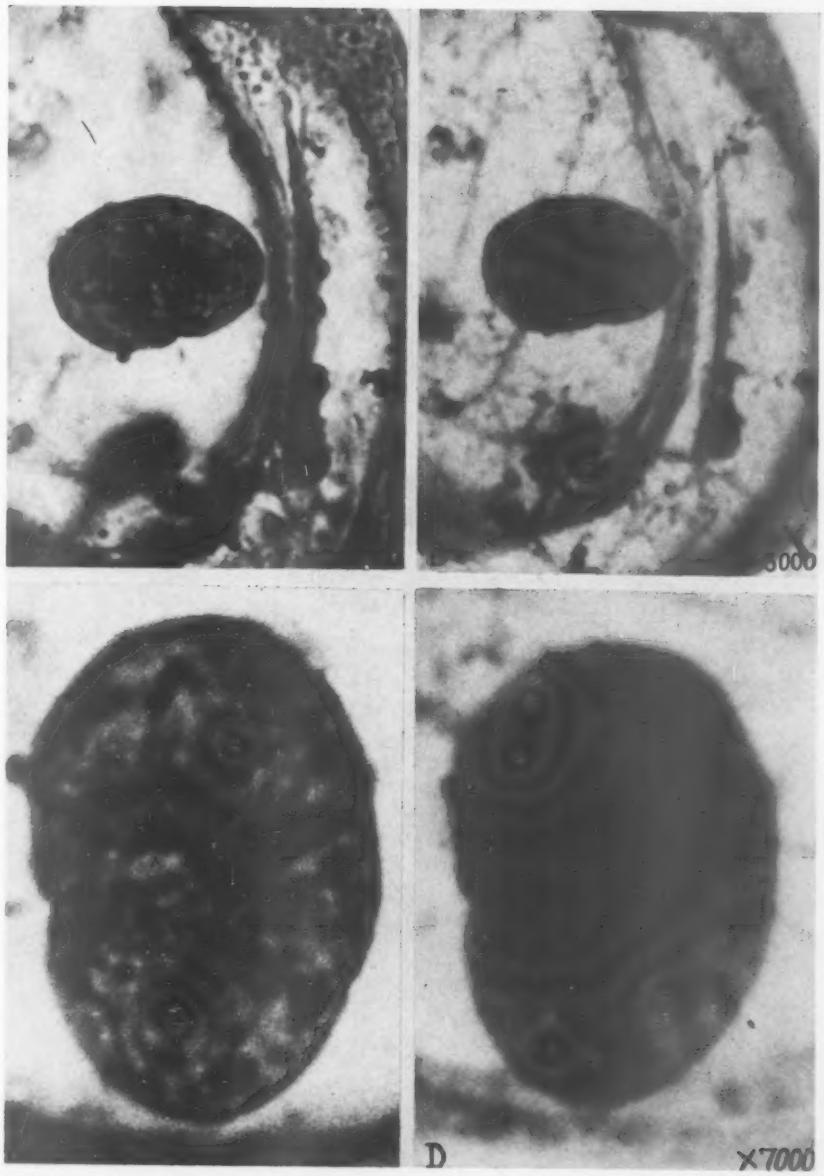


Fig. 8. Enlargements of Fig. 7 under same magnification. *A* and *C*, Nucleus of precancer cell stained with TMK-101. *B* and *D*, Same nucleus of precancer cell stained by Papanicolaou technique. Both groups of photographs show specifically the nuclear changes in size and chromatin distribution.

ness in different pathological conditions of the uterine cervix.[5]

Cellular thickness, or side view of the cells, was observed by the following method:

Cellular material was obtained with a vaginal pipette and a drop was placed at the center of the glass slide. This was followed by the addition of a drop of TMK-101 (undiluted) and mixing with a bacteriological wire loop, without spreading. At the end of 5 minutes, a small drop of ether was added and covered immediately with a cover slip. Upon examination, the fluid mixture showed several active circular movements, similar to the funnel of a tornado. The stained cells move very rapidly in a circular pattern, displaying various surfaces.

Observation of the thickness should be limited to the decrease of the motion in the funnel, as shown in Fig. 6.

With this method, normal cells appear

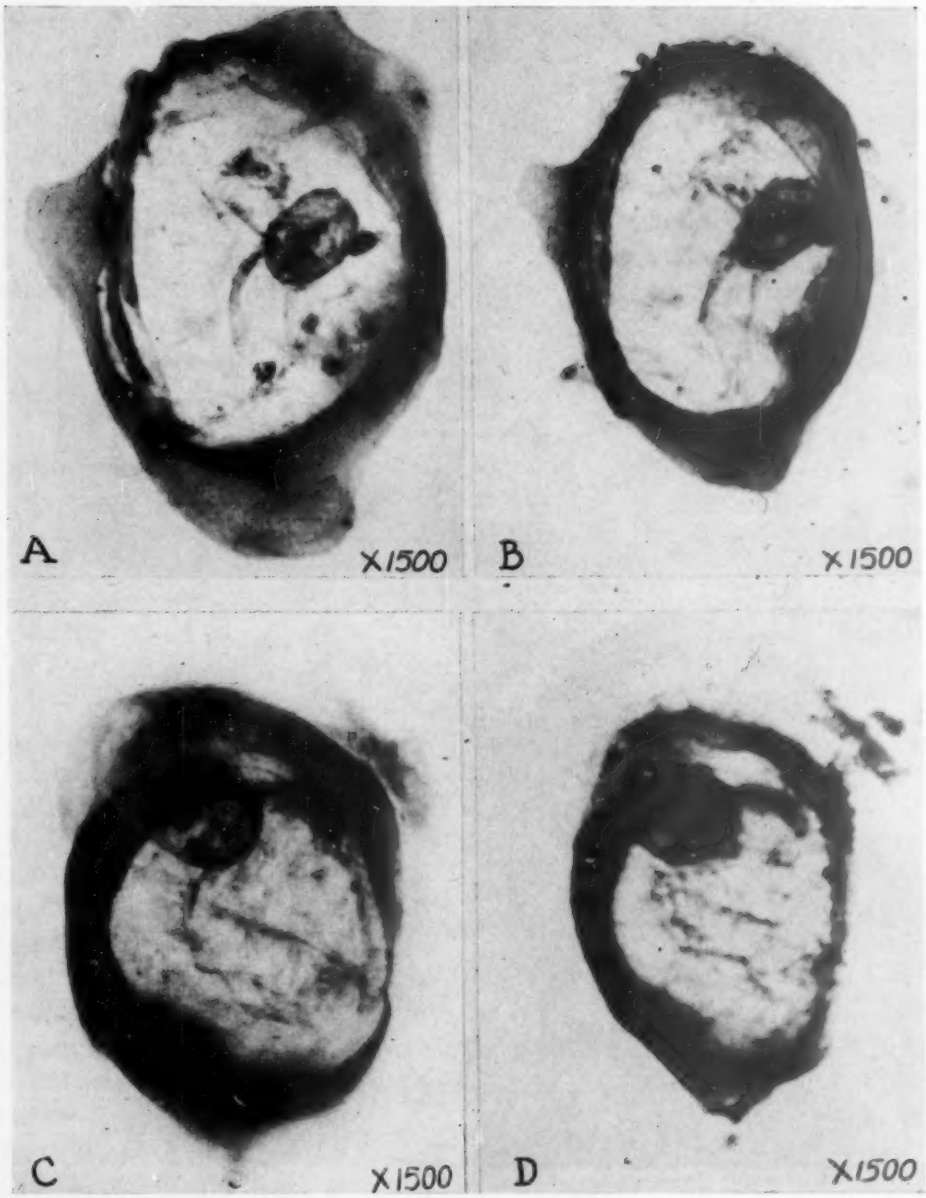


Fig. 9. *A* and *C*, Stained by TMK-101 technique. *B* and *D*, Stained by Papanicolaou technique. Cells *A* and *B* and cells *C* and *D* are the same cells and were photographed under same conditions and magnification. These cells are from precancer cell condition of uterine cervix showing *paranuclear halo*. *A* and *C* show fine details and distinct evidence of membranal defect. *B* and *D* show less detail and other morphological changes due to Papanicolaou technique. This deviation in cellular observation is the reason the perinuclear halo as seen in the precancer cell has become a controversial cytology problem. Scientific cytological research needs a staining procedure which will not mask or change cellular detail.

extremely thin, except in the nuclear area, whereas the precancer cells were much thicker (saucer-shaped).

The volume of the cells stained in TMK-101 solution remained normal and did not vary in size as with various other stains.

Shrinkage or dilatation of the cellular surface was also nonexistent. The morphological characteristics of cells stained in TMK-101 were almost the same as seen under phase contrast.

Fig. 7, *A* and *B*, shows photomicrographs of the same cells from stratified squamous epithelium of uterine cervix. *A* reveals a

normal intermediate cell on the left and a large precancer cell with a paranuclear halo stained with TMK-101. *B* shows the cells stained subsequently by Papanicolaou technique (described under "Material and method").

Comparison of *A* and *B* shows a loss of volume and size and a decreasing of granular material in the cells shown in *B*. *B* displays more translucent and shrunken cellular membranes. The cells were dehydrated to such an extent that the upper and lower surfaces were almost adhered. These conditions, in addition to the very poor cellular detail, proved *B* to be extremely inadequate for cytological research studies.

The paranuclear halo cell in Fig. 7, *A*, in comparison with Fig. 7, *B*, shows a loss in diagonal surface diameter approximately 10 μ (one seventh of the diameter).

In Fig. 7, *A*, the intermediate type cell at left and the peripheral intact portion of the haloed precancer cell have excessive granulation. In Fig. 7, *B*, these granulations disappeared or became less distinct.

The nuclear size varied little, but the chromatin material of nucleus showed extreme variations. The nuclear membranes are quite thin and the karyoplasm is darker in Fig. 7, *B* as compared to Fig. 7, *A*. The most important feature in Fig. 7, *B* is the irregular hyperchromatic and hyperactive appearance of the chromatin clusters located in the nuclei. Fig. 8 shows specifically the nuclear changes in size and in chromatin distribution.

This artificial appearance caused by the staining technique that was used, may bring about a misinterpretation of the smear.

The finely spread nuclear granulation in Fig. 7, *A* is probably chemically coagulated under the effect of strong fixatives. After dehydration, the solution is forced into the cell, thereby causing overstaining in the constricted and condensed portions of the cells. The resulting darkened color can be seen on the right halo border and the nuclei of Fig. 7, *B* cells.

Fig. 9, *A*, *B*, *C*, and *D* are photomicrographs taken under the same conditions. Fig. 9, *B*, and 9, *D* are cells stained subsequently by Papanicolaou technique. Fig. 9, *A* and 9, *C* are the same cells stained previously in TMK-101. These photographs show again the loss and constriction of cellular detail with overstained areas.

The controversial perinuclear halo has been partially elucidated by the use of the TMK-101, "Türk" staining technique in regards to morphological structure (1, 2, 3, and 4).

The photomicrographs which we have discussed were all taken from anaplastic or precancer cellular conditions of the uterine cervix.

Several hundred cells with halos were noticed in the various slides from which the photographs were taken. The halo structures seen in the photographs are significant in the interpretation of other halo cells. Upon examination of Fig. 7, *A*, one can easily see that the halo is a superficial defect of the cell. The cellular membrane displays an irregularly torn surface with some remaining membrane bridges. Cytologists can verify the superficiality of these bridges under the microscope.

In Fig. 7, *B*, the same cells are viewed after Papanicolaou technique, showing relatively little detail. The observer may be misled in believing that the bridges and the halos belong to internal cytoplasmic structure (or defect) caused by metabolic or viral processes. In Fig. 7, *A*, there is negligible cellular depth and we are unable to study the various cellular planes. The membranal bridges, being weak and transparent, usually disappear and become one large halo as in Fig. 7, *B*. Therefore, we can understand where an observer is misled as to the origin of the halo when viewing these cells after fixation.

The intact portion of the halo cell in Fig. 7, *A* is stained homogenously with many cytoplasmic granules whereas the same cell in Fig. 7, *B* is stained irregularly; especially the halo border at the right of the rim of halo is much darker in contrast and the cellular membrane shows much fewer cytoplasmic granules with poorer definition.

Fixation results in dehydration shrinkage and partial condensation of cellular material thereby changing radically the gross cell picture.

Fig. 9, *A* and *C* are similar examples as those given Fig. 7, *A*. This paper is not a discussion of peri- or paranuclear halos, but rather the presentation of the TMK-101, "Türk" staining technique and its effect on cellular structural evaluation.

The halo, which is controversial cytological manifestation in precancer cell stage, is utilized as an example of the better evaluation by use of the TMK-101 stain.

Summary and conclusion

The scientific research value of TMK-101 stain has been studied using uterine cervical smears. The smears are stained with TMK-101 without fixation and are then studied and photographed. These smears are then transferred into fixative solution (50 per cent alcohol absolute and 50 per cent ether) where they undergo staining by Papanicolaou method. These slides are then studied and photographed.

TMK-101, "Türk" staining method has shown to be a much better technique in regard to cytomorphologic research. The photomicrographs show the value of a water-soluble stain in cellular scientific problems (e.g., halos). The TMK-101 dye combination has a water base. The technique requires no fixation, therefore dehydration, shrinkage, condensation, or precipitation of cellular detail is not present.

The acidity of 2 per cent TMK-101 distilled water solution has approximately a pH of 4. This is very close to the normal vaginal acidity and therefore restricts cellular morphological changes.

The experimental observation with TMK-101 can be summarized as such:

1. Cellular details which are very important in the interpretation of malignancy are not seen in the natural condition when stained after fixation in dehydrating dye solution.

2. The photomicrographs of cells stained in TMK-101 have shown that there is a partial mechanical membrane defect on the cells which usually disappears or becomes less visible after fixation.

Therefore, the TMK-101, "Türk" technique provides a new and useful method in cytological research and in the diagnosis of cervical cancer by offering a rapid polychrome staining and keeping the cell structures in three dimensions.

TMK-101, "Türk" staining solutions may be obtained through S & A Laboratories, Inc., P.O. Box 1251, Miami, Florida.

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OBSTETRICS

A comparative study of the alkali reserve of normal and pregnant women

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THERE have appeared in the world literature many articles concerned with the acid-base balance of nonpregnant and pregnant women. Although the consensus of opinion favors the concept that the alkali reserve in pregnancy is lowered, the magnitude of the difference between normal and pregnant subjects remains debatable. It is our feeling that the reason for the disagreement might well be due to the many different ways in which the term "alkali reserve" has been defined and the various methods by which it has been determined.

In the past, a variety of entities have been reported upon and have been variously described as the alkali reserve, the carbon dioxide combining power, and the carbon dioxide capacity of the blood and/or plasma. It should be emphasized that "alkali reserve" is defined as the total carbon dioxide concentration of the blood plasma at a carbon dioxide tension of 40 mm. Hg, the blood being fully saturated with oxygen.

In many reports, the term "alkali reserve" has been used to denote the total carbon dioxide concentration of the blood in vivo, the total bicarbonate concentration of the blood in vivo, the total carbon dioxide or bicarbonate concentration after whole blood has been equilibrated with expired air, the total carbon dioxide or bicarbonate concentration after either blood or plasma has been equilibrated with alveolar air, 5 per cent carbon dioxide mixtures, or 5.5 per cent carbon dioxide gas mixtures. Reports have also appeared in which investigators have taken the Haldane effect into account and have reported "alkali reserve" data corrected for various degrees of oxygen unsaturation of the blood in vivo. It would appear that the use of so many different methods might well lead to the lack of uniformity in results that have been obtained.

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The reported data are apt to be confusing and in disagreement for another reason. If one critically evaluates some of the above-mentioned procedures, it will be noted that they have serious weaknesses. For example, the equilibration of blood or plasma with any sample of expired air gives no indication of the P_{CO_2} with which the blood or plasma has been equilibrated. The use of alveolar air for equilibration of the sample is apt to come closer to a P_{CO_2} of 40.0 mm. than any sample of expired air, provided the individual performing the procedure is not pregnant (in which case the P_{CO_2} of alveolar air will be approximately 33.0 mm.), provided the person is not in the postovulatory phase of the menstrual cycle (the P_{CO_2} alveolar air is more likely to be of the order of 36.0 mm.) and provided he or she has not recently eaten, smoked, and/or exercised. The use of a 5 per cent carbon dioxide gas mixture will yield a P_{CO_2} of approximately 35.5 mm. Hg and the use of a 5.5 per cent gas mixture is still unlikely to yield a P_{CO_2} of 40.0 mm.

All of the above-mentioned techniques have the further drawback that unless determinations are performed at sea level, the decreased barometric pressure at high altitude will produce considerable additional error. High altitude results would tend to give too low a value for the alkali reserve, and, accordingly, comparison of sea level data with results at any altitude is not possible. The use of the Haldane effect in reporting alkali reserve data leads to further confusion, for the results will reflect the degree of oxygen unsaturation of the blood sampled.

In view of the above-mentioned reasons and because of the importance of acid-base balance in regard to oxygenation of the fetus, it was considered advisable to reinvestigate the problem, using the strict definition of alkali reserve—*the total carbon dioxide concentration of the blood plasma at a carbon dioxide tension of 40.0 mm. Hg with the blood fully oxygenated.*

Materials and methods

All of the pregnant patients were registered for prenatal care and delivery at the Johns Hopkins Hospital. The nonpregnant subjects were on the gynecological service, and, with one exception (Patient S. H.), absence of pregnancy was assured—these women had all undergone hysterectomies.

Eighteen milliliters of blood was drawn anaerobically from an antecubital vein into oiled syringes which contained a solution of potassium oxalate and ammonium fluoride (2 per cent $K_2C_2O_4$ and 0.6 per cent NH_4F). The final mixture contained nine parts of blood and one part of the anticoagulant.

The specimen was introduced into 250 ml. tonometers by a puncture through a rubber sleeve stopper which closed one end of the tonometer. For each alkali reserve determination 2 tonometers were used and, into each, 10 ml. of the blood-anticoagulant mixture was inserted. One tonometer contained room air and approximately 35.0 mm. Hg of carbon dioxide pressure, and the other room air and approximately 45.0 mm. Hg.

The tonometers were rotated for 15 minutes in a constant temperature water bath at 38° C. After this period of time, the total gas pressure in each tonometer was equilibrated with atmospheric pressure by opening the stopcock with its tip just below the surface of the water in the bath. At this moment the barometric pressure was read. The tonometers were then rotated for another 15 minutes, thereby allowing re-equilibration of the blood and the gas mixture at atmospheric pressure.

The samples of blood were then collected anaerobically from the tonometers into oiled syringes and were transferred under oil to centrifuge tubes. Centrifugation was carried out for 30 minutes at 2,500 r.p.m.

The plasma from these specimens was anaerobically collected into oiled syringes, and the total carbon dioxide content of each specimen was determined in duplicate on 0.5 ml. samples according to the method of Van Slyke and Neill.[1]

The carbon dioxide concentration (CO_2) in each tonometer was measured by the method of Scholander.[2] The carbon dioxide pressure (P_{CO_2}) was calculated from the carbon dioxide concentration and the barom-

ric pressure. The latter value equals the total barometric pressure read at the time of equilibration of the sample minus the water vapor pressure:

$$P_{CO_2} = (co_2) \times (\text{total barometric pressure} - \text{water vapor pressure}) \quad (1)$$

The physically dissolved carbon dioxide in each sample was obtained by multiplying the carbon dioxide pressure in each tonometer by the coefficient of solubility for carbon dioxide (0.0301 mM. per liter per mm. Hg of carbon dioxide pressure):

$$\text{Physically dissolved } CO_2 = (P_{CO_2})\ (0.0301) \quad (2)$$

The bicarbonate content of each specimen was determined by subtracting the physically dissolved carbon dioxide from the plasma carbon dioxide content:

$$BHCO_3 \text{ (uncorrected)} = \text{total } CO_2 - \text{physically dissolved } CO_2 \quad (3)$$

To account for the dilution by the anticoagulant (2 parts of 2 per cent $K_2C_2O_4$ × 0.6 per cent NH_4F and 18 parts of blood), the calculated bicarbonate was multiplied by 10/9; this figure represents the corrected bicarbonate concentration.

$$BHCO_3 \text{ corrected} = (BHCO_3 \text{ uncorrected}) \left(\frac{10}{9}\right) \quad (4)$$

In turn, the physically dissolved carbon dioxide was added to the undiluted bicarbonate concentration yielding the corrected total carbon dioxide content of the plasma sample:

$$\text{Total } CO_2 \text{ corrected} = \text{physically dissolved } CO_2 + BHCO_3 \text{ corrected} \quad (5)$$

The corrected total plasma carbon dioxide content was then plotted on graph paper along with the carbon dioxide pressure with which the sample had been equilibrated. In this manner one total carbon dioxide content at a pressure below 40.0 mm. P_{CO_2} and one at a pressure above 40.0 mm. P_{CO_2} results. If one assumes that the carbon dioxide dissociation curve of maternal blood is a straight line between P_{CO_2} 35.0 mm. and 45.0 mm., then interpolation of these two points gives the total carbon dioxide content of the plasma at a P_{CO_2} of 40.0 mm. Hg, i.e., "the alkali reserve."

Results

In Table I, the data obtained in 14 nonpregnant women are shown. The mean alkali reserve in this group was 25.3 mM. per liter (standard error of the mean, 0.3). By use of the Henderson-Hasselbalch equation:

$$pH = 6.10 + \log \frac{\text{bicarbonate}}{\text{dissolved } CO_2} \quad (6)$$

The pH at P_{CO_2} 40.0 mm. Hg was calculated, and the mean value for this series equaled 7.40.

The results obtained in 23 gravidas, chosen at random to represent the span of pregnancy, are presented in Table II. The mean alkali reserve in this group equaled 22.0 mM. per liter (standard error of mean 0.17)—a value significantly lower than that for the mean nonpregnant one. The mean calculated pH at P_{CO_2} 40.0 mm. Hg was 7.34 (nonpregnant = 7.40). The last reported case (S. H.) is of interest in that this patient, originally believed *not* pregnant, had not undergone a hysterectomy. The alkali reserve, 21.0 mM. per liter, fell considerably below the range for nonpregnant women. She underwent a dilatation and curettage, the preoperative diagnosis being dysfunctional uterine bleeding. Microscopic examination of the tissue, however, revealed placenta. Thus, this patient was in fact pregnant (as her alkali reserve had suggested).

In an attempt to determine the variability in alkali reserve in a given individual throughout the course of pregnancy, 2 patients (M. D. and L. P.) were evaluated from the tenth to the thirty-sixth week. The results obtained are reported in Table III. M. D. showed a mean alkali reserve of 22.9 mM. per liter (standard error of mean 0.31) and a calculated mean pH at P_{CO_2} 40.0 mm. Hg of 7.36. L. P. had a mean alkali reserve of 22.1 mM. per liter (standard error or mean 0.31) and a calculated mean pH at P_{CO_2} 40.0 mm. Hg of 7.34.

In Table IV, the mean values for all pregnant and nonpregnant subjects are presented. In the former, the alkali reserve equaled 21.0 mM. per liter and, in the latter, 24.1 mM. per liter—a difference of 3.1 mM. per liter. In the pregnant series the calculated pH at P_{CO_2} 40.0 mm. Hg was 7.34, and it was 7.40 in the nonpregnant.

All the points obtained are plotted in Fig. 1. As may be seen, the values obtained in the two groups do not overlap except for a single case. All alkali reserves obtained in the pregnant series ranged from 20.5 to 24.0 mM. per liter, while the nonpregnant values, barring the one single exception, fell between 24.1 and 27.0 mM. per liter.

Table I. Total plasma carbon dioxide content in nonpregnant group

	CO_2 pressure (mm. Hg)	Physically dissolved CO_2 (mM./L.)	Total plasma $BHCO_3$ (mM./L.)	Total plasma CO_2 (mM./L.)	$\frac{BHCO_3}{\text{dissolved } CO_2}$ (mM./L.)	pH at P_{CO_2} 40 mm. Hg
	40	1.2	21.8	23.0	18.17	7.36
	40	1.2	24.8	26.0	20.66	7.42
	40	1.2	24.8	26.0	20.66	7.42
	40	1.2	24.8	26.0	20.66	7.42
	40	1.2	23.6	24.8	19.66	7.39
	40	1.2	22.9	24.1	19.08	7.38
	40	1.2	23.9	25.1	19.91	7.40
	40	1.2	24.3	25.5	20.25	7.41
	40	1.2	25.8	27.0	21.50	7.43
	40	1.2	25.8	27.0	21.50	7.43
	40	1.2	22.9	24.1	19.08	7.38
	40	1.2	24.1	25.3	20.09	7.40
	40	1.2	24.4	25.6	20.33	7.41
	40	1.2	23.8	24.7	19.58	7.39
Mean values	40	1.2	24.1	25.3	20.09	7.40

Table II. Total plasma carbon dioxide content in pregnant group

Duration of gestation (weeks)	CO_2 pressure (mm. Hg)	Physically dissolved CO_2 (mM./L.)	Total plasma $BHCO_3$ (mM./L.)	Total plasma CO_2 (mM./L.)	$\frac{BHCO_3}{\text{dissolved } CO_2}$ (mM./L.)	pH at P_{CO_2} 40 mm. Hg
9	40	1.2	21.8	23.0	18.16	7.36
12	40	1.2	21.9	23.1	18.25	7.36
14	40	1.2	21.1	22.3	17.58	7.35
19	40	1.2	20.6	21.8	17.17	7.33
20	40	1.2	21.7	22.9	18.08	7.36
22	40	1.2	21.6	22.8	18.00	7.36
23	40	1.2	19.7	20.9	16.42	7.32
24	40	1.2	21.8	23.0	18.16	7.36
25	40	1.2	21.8	23.0	18.16	7.36
26	40	1.2	20.6	21.8	17.17	7.33
27	40	1.2	21.6	22.8	18.00	7.36
30	40	1.2	20.9	22.1	17.41	7.34
32	40	1.2	20.7	21.9	17.25	7.34
32	40	1.2	20.8	22.0	17.33	7.34
34	40	1.2	20.0	21.2	16.66	7.32
35	40	1.2	20.5	21.7	17.08	7.33
36	40	1.2	19.3	20.5	16.08	7.31
37	40	1.2	19.8	21.0	16.55	7.32
39	40	1.2	19.6	20.8	16.32	7.31
41	40	1.2	21.2	22.4	17.66	7.35
42	40	1.2	19.8	21.0	16.55	7.32
44	40	1.2	20.8	22.0	17.33	7.34
S. H.	40	1.2	19.8	21.0	16.50	7.32
Mean values	40	1.2	20.8	22.0	17.30	7.34

Table III. Total plasma carbon dioxide content in pregnant patients M. D. and L. P.

Duration of gestation	*CO_2 pressure (mm. Hg)*	*Physically dissolved CO_2 (mM./L.)*	*Total plasma $BHCO_3$ (mM./L.)*	*Total plasma CO_2 (mM./L.)*	*$\frac{BHCO_3}{\text{dissolved } CO_2}$ (mM./L.)*	*pH at P_{CO_2} 40.0 mm. Hg*
Patient M. D.						
10	40	1.2	22.5	23.7	18.75	7.37
14	40	1.2	20.8	22.0	17.33	7.34
18	40	1.2	22.8	24.0	19.00	7.38
22	40	1.2	20.8	22.0	17.33	7.34
26	40	1.2	21.8	23.0	18.16	7.36
29	40	1.2	21.8	23.0	18.16	7.36
34	40	1.2	22.2	23.4	18.50	7.37
36	40	1.2	20.8	22.0	17.33	7.34
Mean values	40	1.2	21.7	22.9	18.07	7.36
Patient L. P.						
11	40	1.2	21.8	23.0	18.16	7.36
15	40	1.2	22.3	23.5	18.58	7.37
19	40	1.2	19.9	21.1	16.58	7.32
23	40	1.2	21.1	22.3	17.58	7.35
26	40	1.2	20.3	21.5	16.91	7.33
31	40	1.2	21.1	22.3	17.58	7.35
33	40	1.2	19.8	21.0	16.55	7.32
36	40	1.2	20.8	22.0	17.33	7.34
Mean values	40	1.2	20.9	22.1	17.41	7.34

Table IV. Mean data obtained on pregnant and nonpregnant subjects

	Total plasma $BHCO_3$ (mM./L.)	*Total plasma CO_2 (mM./L.)*	*$\frac{BHCO_3}{\text{dissolved } CO_2}$ (mM./L.)*	*pH at P_{CO_2} 40 mm. Hg*
Mean for all pregnant women	21.0	22.2	17.50	7.34
Mean for all nonpregnant women	24.1	25.3	20.09	7.40

Comment

Since the pioneer studies of Keys,[3] there is found in obstetric literature frequent mention of the state of metabolic acidosis that occurs in gravidas during the course of pregnancy. Initially, this belief received support from studies which demonstrated an increased ammonia coefficient and the ease of ketonuria production in pregnant women.[4-6] Bokelmann and Bock[7] believed that acidosis in gestation existed, for they found that the blood acetone level of pregnant subjects on a high-fat diet increased 63 per cent, while that of normal individuals increased only 10 per cent. Bokelmann[8] also found an elevation of 2.7 mg. per cent in the blood lactic acid level in pregnancy, and Zangemeister,[9] using the titration method of Zuntz, reported a reduction in total blood alkalinity in gestation.

The concept of a pregnancy acidosis received further support by studies related to the oxygen dissociation curve of adult blood, for several groups of investigators[10-12] reported that the curves of blood of pregnant women were shifted to the right of the nonpregnant—a finding which would be compatible with maternal acidosis. In regard to experimental technique, it is important to mention the fact that the curves previously referred to were constructed at a constant P_{CO_2} and not at a constant pH, and the P_{CO_2} employed was usually 40.0 mm. Hg. This value was chosen for it was assumed

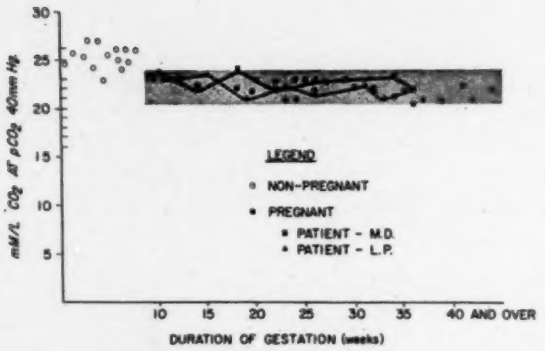


Fig. 1. Alkali reserve of nonpregnant and pregnant women.

that gravidas, like their nonpregnant counterparts, had P_{CO_2}'s in the arterial blood of 40.0 mm. Hg. This assumption, however, was an error, for several researchers[13-24] have demonstrated that the arterial P_{CO_2} of the pregnant woman is only around 32.0 mm. Hg.

In regard to this problem of pregnancy acidosis, the work of Hasselbalch[13] is of particular significance because he measured the alveolar carbon dioxide pressure in a single subject (Haldane method) and found it to be of the order of 31.0 mm. Hg. In association with Gammeltoft,[14] he extended his studies, confirmed his previous findings, and postulated an increased acid production in pregnancy which was compensated by a lowered alveolar P_{CO_2}. This hypothesis was based upon the fact that measurements of pH, performed electrometrically, equaled 7.41 for maternal arterial blood at 37° C. In turn, Doring and Loeschke[15] raised the question of whether the lowered alveolar P_{CO_2} might be due to hyperventilation, the latter being secondary to the increased progesterone production which accompanies gestation. Along these lines it is of interest that, as early as 1915, Hasselbalch and Gammeltoft[14] had noted a decreased alveolar P_{CO_2} in the postovulatory phase of the menstrual cycle. The significance of progesterone as an important factor was further enhanced by the work of Heerhaber and associates,[16] who administered this steroid to males and one postmenopausal woman, and found reductions in alveolar P_{CO_2}. In regard to the possible effect of estrogens, Doring and associates[24] reported a similar decrease in alveolar P_{CO_2} but of lesser magnitude.

Since many investigators have found the pH of pregnant women to be unchanged, the concept is now generally accepted that progesterone causes hyperventilation. This set of circumstances would lead to a respiratory alkalosis were it not for the fact that there is a lowering of the plasma concentration of bicarbonate. As a result, the pH is maintained at about 7.40.

The lowered alkali reserve which occurs in pregnancy is, therefore, a compensation for a respiratory alkalosis. The data presented in this investigation confirm this concept in that the alkali reserve reported herein would give a pH of 7.34 at a P_{CO_2} of 40.0 mm. Hg, while in the presence of a pH of 7.40 the data would yield a P_{CO_2} of 34.0 to 35.0 mm. Hg for antecubital vein blood.

In regard to the magnitude of the change in alkali reserve during pregnancy, comparison of the results reported herein and those of other investigators is difficult because of differences in methodology. For example, by reference to carbon dioxide dissociation curves of maternal blood, it may be seen that Haselhorst and Stromberger[10] obtained an alkali reserve of about 22.0 mM. per liter. Their experiments, however, were performed with tonometers filled with a P_{O_2} of only 40 mm. Hg. From work previously reported,[25] we have found that this P_{O_2} would be insufficient to fully saturate the blood hemoglobin with oxygen. Leibson and collaborators[12] constructed their carbon dioxide dissociation curves at a P_{O_2} of 30.0 mm. Hg by measuring the blood carbon dioxide content and by using Van Slyke and Sendroy's nomogram to extrapolate for plasma values. By this method they reported the alkali reserve to equal 16.2 mM. per liter. It should be mentioned that the specimens of blood that they obtained were collected after vaginal delivery, and one would expect a lowering of the alkali reserve at this time because of the displacement of bicarbonate by fixed acids. Eastman and associates,[11] using blood also obtained at vaginal delivery and correcting for oxygen unsaturation of the blood in

vivo, reported a total carbon dioxide content of the plasma at P_{CO_2} 40.0 mm. Hg of 18.4 mM. per liter. Darling and associates[26] found an alkali reserve of 20.0 mM. per liter but obtained their results indirectly, corrected them to "normal lactate levels," and collected bloods at the time of vaginal delivery. Bartels[27] stated that Rossier and Hotz demonstrated a total carbon dioxide content at P_{CO_2} 40.0 mm. Hg of 20.1 mM. per liter, but the source and time of collection of the blood specimen is not known.

Summary

It may be stated that we have found the alkali reserve in pregnancy to be lowered. The data submitted in this report supply values which were determined by using standard techniques, and the results obtained allow us to employ the term "alkali reserve" in accordance with the standard definition, i.e., the total carbon dioxide concentration of blood plasma at a P_{CO_2} of 40.0 mm. Hg, the blood hemoglobin being fully saturated with oxygen.

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Electrophoretic mobility of the red blood cell during human pregnancy

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THE literature on the cataphoretic velocity of erythrocytes in human pregnancy contains data on 4 women at term.[1] This showed values interpreted as normal and it was concluded that pregnancy did not have any influence upon the electrophoretic properties of red cells. In the course of a study of the electrophoretic behavior of the red cell in a variety of clinical conditions, we accumulated from 100 women in various stages of pregnancy data showing that the mobility of the red cell does change. Since our data are based on tests involving a relatively large number of women of different ages, at different stages of gestation, we believe our conclusions have greater validity than those based upon the earlier work.

Historical review

Electrophoresis, which pertains to the movement of particles in an electric field, is one aspect of the more generalized phenomenon of electrokinetics[2-4] which also consists of electroosmosis and streaming potential. The particles may be protein molecules, colloid particles, viruses, bacteria, or animal cells.

The physical chemistry involved in electrophoresis was developed by Reus in 1807, Quincke in 1861, Helmholtz in 1871, and Hardy in 1905.[5] The theory and development of the mathematical formulas have been treated by many authors.[2, 3, 5-7]

The microelectric cell used by investigators throughout the years was developed by Northrop and Kunitz in 1925 and modified by Abramson,[8] Briggs,[7] and Ponder.[9] Pioneer work on the red blood cell was done at various times by a small group of men—Abramson, Moyer, Furchgott, Gorin, and Ponder.[1, 10-13] It was established in 1929[1] that the mammalian red cell had a negative charge and moved in an electric field, and that the mobility varied from species to species but, within a given species, was constant and not affected by the size or shape of the blood cell. The mobility of the red cell of human beings was found to be 1.3 μ per second per volt per centimeter; that of the rabbit, pig, and guinea pig lower, and that of the monkey, mouse, and cat higher.

Furchgott and Ponder[12] concluded that the surface of the red cell is largely lipid and dominated by acid groups, possibly phosphorus. From another study Abramson, Gorin and Ponder,[13] concluded that the surface is hilly and that it has valleys no deeper than 1 Å. in radius. Some interesting data

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have been collected from changes in mobility, caused by substances such as antibodies or viruses[15, 16] adsorbing to the surface of the red cell, and from alteration of the surface by x-irradiation or chemicals.[14, 17] The isoelectric point of the red cell membrane[11, 18] has received attention but it is difficult to determine because at the pH necessary to produce a change in the sign the cell dies. Nevertheless, Ponder and Ponder[9] believe they have established this point as pH 2.0 or lower.

Several papers have appeared on mobility values for normal human beings at pH 7. Abramson[1] obtained 1.31 ± 0.02 μ per second per volt; Furchgott and Ponder,[12] 1.03; Crager, Tully, and Hansen,[19] using a buffer of 7.35, obtained 1.31 ± 0.04 for blood types A and B, 1.52 ± 0.09 for type O, and 1.37 ± 0.05 for type AB. Two persons in our laboratory ran separate series of tests. One series was composed of 121 persons and the value obtained was 1.32 ± 0.05. The other series was composed of 76 persons and the value was 1.27 ± 0.05.[20]

Method of study

The technique we employed has been described in detail elsewhere.[20] Briefly, we employed the vertical cell and the technique described by Ponder.[9] Using a Veronal buffer system, we made determinations at pH 9, 7, 5.5, and 4. The ionic strength of the solution was constant at 0.172. We found that meticulous attention to technique was necessary. It is highly important that the electrical system should function properly, that solutions be prepared precisely and remain constant, that glassware be absolutely clean, and that the apparatus be set on a vibration-free base. Temperature control of the area of operation is important; a draft blowing upon the apparatus causes eddy currents. Coated electrodes are a source of trouble and they must be cleaned constantly. The light source must be cool. Schmoluchowski, quoted by Brinton and Lauffer,[6] discovered that the point at which the red cell is focused for mobility measurement is of critical importance; for our cell this point is 0.21 mm. beyond the inner surface of the anterior plate.

Blood was collected from 100 pregnant women, predominantly Puerto Rican, 18 to 32 years of age and one 44 years old. Duration of pregnancy at the time blood was withdrawn varied from 2 months (5 women) to 9 months (29 women); in the periods 3 and 8 months there were 11 women. Specimens were also obtained from 18 women during or immediately after delivery. In addition, we made determinations on 29 specimens obtained from the umbilical cord of the placenta immediately after delivery, upon 4 specimens from women with the toxemia of pregnancy, upon one specimen from a woman with hydatid mole, and upon one who was carrying a fetus that had been dead 5½ weeks. We also studied blood from one woman before and during menstruation.

Results

At 4 pH levels (9, 7, 5.5, 4) and regardless of race or age, the mobility of the red cell in pregnancy proved to be slower than that of the cells of the normal control group, as shown in Table I. In 88 per cent of the nonpregnant group the mobility was above 1.25, while in the pregnant group it was below 1.25 in 100 per cent of cases. In the nonpregnant group the mobility for 10 per cent of the women was between 1.21 and 1.25, contrasted with a like mobility for

Table I. Electrophoretic mobility of pregnant women and normal controls

	pH			
	9	*7*	*5.5*	*4*
Series 1 (121 persons)	1.30 ± .03	1.32 ± .05	1.06 ± .11	0.87 ± .13
Series 2 (79 persons)	1.33 ± .05	1.27 ± .05	1.16 ± .04	1.08 ± .08
Pregnancy (100 persons)	1.21 ± .02	1.13 ± .03	1.06 ± .03	1.00 ± .03

74 per cent of pregnant women; the mobility for the remaining 26 per cent of pregnant women was below 1.21.

We had no patients in an earlier stage of pregnancy than 2 months and could therefore not determine how soon after conception the change in red cell mobility begins. In the 4 cases of 2 months post-conception, the mobility was low. The values are included in Table II and are seen to be essentially the same as the values at all other stages of pregnancy. We had 12 patients at term, all with the low values characteristic of the group as a whole. Determinations on 2 of them showed that the mobility returns to normal 24 hours after delivery.

Of possible significance in understanding the relationship of pregnancy to the observed changes in electrophoretic mobility of the red cell was a single determination done on cells of a woman immediately after she had passed a dead fetus. No fetal heartbeat had been heard for 5½ weeks and the mobility values before the abortion were normal. Reciprocally related to this observation, perhaps, is one made in the case of another woman who had already aborted and who had persistent bleeding. Her mobility values were lowered. Later a hydatid mole was passed.

A study was begun on red cells obtained from 4 patients with diagnoses of toxemia of pregnancy. Very interestingly, the mobilities at pH 9 and 7 were within the normal range, while those at pH 5.5 and 4 were distinctly elevated. Since in no other condition has this as yet been noted, we consider it worth reporting at this time (Table III).

Table II. Electrophoretic mobility in second month of pregnancy

pH			
9	*7*	*5.5*	*4*
1.25	1.17	1.45	1.00
1.21	1.10	0.98	0.94
1.21	1.14	1.10	1.03
1.21	1.12	1.03	0.98

Table III. Electrophoretic mobility in toxemia of pregnancy

	pH			
	9	*7*	*5.5*	*4*
Patient 1	1.30	1.05	1.19	1.21
Patient 2	1.28	1.14	1.05	1.28
Patient 3	1.25	1.19	1.33	1.23
Patient 4	1.33	1.28	1.14	1.12

Table IV. Electrophoretic mobility from umbilical cord

	pH			
	9	*7*	*5.5*	*4*
Mean	1.40	1.34	1.18	1.09
Standard deviation	0.03	0.04	0.08	0.10

In view of the observed change in electrophoretic mobility of the red cell in pregnancy, we were interested in the behavior of placental cells. For this study, blood was obtained from the umbilical cord of 29 placentas immediately after delivery. The mobilities were found to be not slow, as in the mother, but distinctly and significantly higher than normal, which was an interesting finding (Table IV).

Determinations were next made on blood withdrawn simultaneously from the umbilical cords and the heels of 2 infants immediately after delivery. The values were identically high in cord and infant. Forty-eight hours later the electrophoretic mobility of the infants' blood had returned to normal.

Comment

Generally, when two surfaces come into contact, there is a separation of electrostatic charge, one surface becoming negative in respect to the other. In the case of the red blood cell, its surface becomes negative in respect to the surface of the fluid with which it is in contact. These surfaces of opposite charge constitute an electric double layer. It was Helmholtz[5] who drew an

analogy between this double layer and a condenser and derived therefrom the physical principles for electrophoresis.

When an electromotive force is applied, the positive and negative portions of the double layer are displaced relative to each other. The red cell, for example, migrates to the anode and this migration constitutes the phenomenon of electrophoretic mobility. The velocity at which the red cell moves per second per unit of electricity per unit of volume of the electrophoresis chamber, containing the red cells, is the mobility. Therefore, the mobility of the red cell reflects the amount of electrical charge on its surface and it will move slow or fast depending on the quantity of the charge. Since also environmental factors affect charge and hence mobility, these must be kept constant. These factors are temperature of the solution and external environment, voltage, electric current, pH, ionic strength, and protection against vibration and drafts. If a standardized technique is followed with meticulous care, reliable, reproducible results are obtainable. The sensitivity of the method is such that an increase or decrease of mobility at pH 9 or 7 greater than 0.1 μ per second per volt per centimeter is significant.

In pregnancy, the red cell mobility is approximately 0.2 μ less than normal. This was found to be true in 100 per cent of determinations made upon 100 women. The change was found to take place as early as 2 months. It may occur earlier but we were not able to determine this because we had no subjects in an earlier stage of pregnancy. The mobility remains slow throughout pregnancy and through labor and returns to normal approximately 24 hours after delivery. The presence of live villi appears to be one factor related to the slowing of red cell mobility since a patient with hydatid mole had the pattern characteristic of normal pregnancy. Death of the fetus reversed to normal the pattern of the one patient who came under observation because there had been no sound from the fetal heart for 5½ weeks.

The significance of the change in the surface of the red cell, responsible for the slowing of its mobility, remains to be established. Cells of 4 patients with the toxemia of pregnancy showed increased mobility at pH 5.5 and 4. It is important that the meaning of this be established. Also deserving of further study is the fact that mobility of cells from the umbilical cord accelerates while that of cells taken almost simultaneously from the mother retards to less than normal.

It would be interesting to study how soon after conception the change in mobility occurs, since this might be used as a marker for some early stage in pregnancy. As a diagnostic criterion for pregnancy, electrophoretic mobility has the drawback of being a nonspecific reaction.

We have not determined what it is that causes slowing of the red cells in pregnancy. We suspect that it is a serum factor, judging from the fact that we have demonstrated the presence of such a factor in the sera of patients with Hodgkin's disease, whose cells likewise manifest reduced mobility.

Summary

1. The electrophoretic mobility of the red cells of normal human beings has been established at pH 9, 7, 5.5, and 4 and found to be constant regardless of age, sex, or race.

2. Early in pregnancy, the electrophoretic mobility of the red cell becomes slower than normal and remains so until approximately 24 hours after delivery, when it returns to normal.

3. It is considered probable that a serum factor is responsible for this slowing.

4. In toxemia of pregnancy, the red cell mobility increases at pH 5.5 and 4.

5. The mobility of cells from the umbilical cord and cells of the newborn infant is abnormally rapid at pH 5.5 and 4.

6. The meaning of the changes in mobility of the red blood cells during pregnancy remains to be determined.

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Changes in vitamin B_6 during pregnancy

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IN 1942 vitamin B_6 was first administered during pregnancy for the treatment of hyperemesis gravidarum.[1] Since that time, there has been an increasing body of information that has demonstrated its importance in fertility, gestation, normal fetal development, and prevention of some of the complications of pregnancy.

Although the absolute figures for the minimum daily requirement of vitamin B_6 have not as yet been established, present research suggests that it may lie in the range of 2.0 mg. ± 0.5 mg. On this basis, it may be categorically stated that the usual diet in the United States contains borderline quantities of vitamin B_6, with a content of 1.5 mg. ± 0.5 mg. per day.[2] Furthermore, studies of diet during pregnancy carried out by Hobson in 1948 and more recently by McGanity in 1954 have shown a daily intake of 1.0 mg. ± 0.5 mg.[3, 4] It would therefore appear that, although the usual diet during pregnancy is not grossly deficient in vitamin B_6, it may not be entirely adequate to meet the requirements of mother and fetus.

The successful use of vitamin B_6 in the treatment of nausea and vomiting in the first trimester was at first based entirely on clinical observations. However, in 1949, McGanity demonstrated that during this period the pregnant woman had abnormally low blood urea nitrogen levels and showed an abnormal response with marked increases in blood urea nitrogen following ingestion of alanine.[5] Both of these extremes reverted to normal by the administration of vitamin B_6. Beaton found that there was a marked increase in the fasting plasma glutamic acid levels during the first trimester which also could be corrected by vitamin B_6.[6]

Wachstein has endeavored to establish a more quantitative estimate of B_6 requirements by adapting the xanthurenic acid excretion test to problems in pregnancy.[7] Using a loading test of 10 Gm. of DL-tryptophan orally, he has found a marked increase in xanthurenic acid excretion during pregnancy. This has been interpreted as resulting from insufficient B_6 to permit tryptophan to follow its normal pathways of degradation. His group has accumulated data indicating further increases in xanthurenic acid excretion late in pregnancy. Even higher excretion was reported during toxemia and preeclampsia.[8] Treatment with vitamin B_6 corrected the excessive xanthurenic acid excretion, indicating that an adequate balance of the vitamin had been restored. A number of other workers have confirmed and extended these observations and have suggested that from 10 to 25 mg. of vitamin B_6 may be required daily in order to prevent the abnormal xanthurenic acid excretion during pregnancy.[9-11]

Several other techniques have been devised in an effort to obtain more information concerning this problem. These have included measurement of urinary pyridoxic acid excretion, blood transaminases, and pyridoxal phosphate in plasma and white

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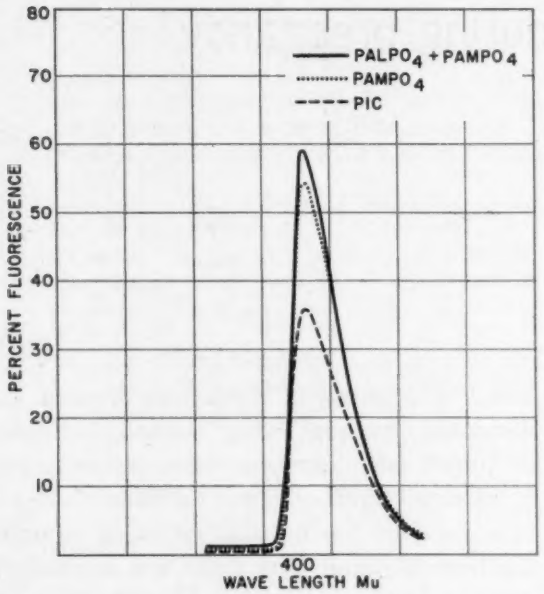


Fig. 1. Typical fluorescence curves of the vitamin B_6 group.

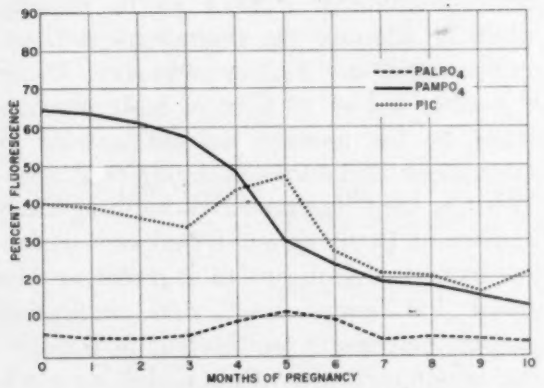


Fig. 2. Controls receiving no additional vitamin B_6.

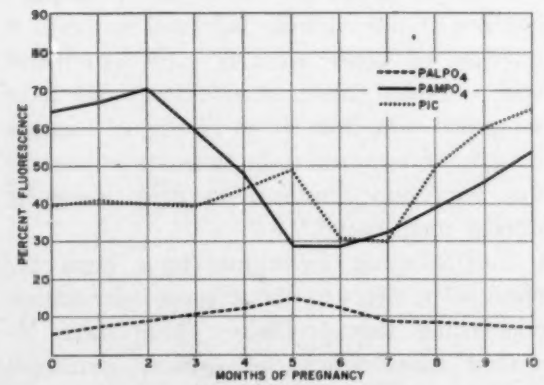


Fig. 3. Patients receiving 6 mg. of vitamin B_6 daily.

blood cells.[12-14] The findings by all of these procedures support the thesis that there is an increased vitamin B_6 requirement during pregnancy.

The importance of the availability of an adequate supply of vitamin B_6 to the fetus has been amply demonstrated by experimental work in animals using vitamin B_6–deficient diets and antimetabolites such as desoxypyridoxine. Using these techniques, Nelson and associates, and later McGanity and co-workers, showed that an established B_6 deficiency in the pregnant female rat resulted in resorption of embryos or production of malformed fetuses.[15, 16] Nelson and Evans have postulated that the faulty mechanisms involved under these circumstances include the pituitary and ovarian hormones. They have noted that although the animals produce adequate, if not excessive follicle-stimulating hormones and interstitial cell–stimulating hormones, they do not appear to be capable of releasing or utilizing them.[17] Ross and associates[18] have extensively explored the nutritional aspects of this problem in rats and have made similar observations. Furthermore, they found evidence suggesting that vitamin B_6 intake prior to pregnancy, as well as continued adequate intake during gestation, was of importance.

Methods and materials

The spectrophotofluorometric procedure that has been previously described for measuring vitamin B_6 in biologic samples has been further modified and extended to provide a profile of vitamin B_6 activity.[19] The technique permits the separation of pyridoxal phosphate ($PALPO_4$), pyridoxamine phosphate ($PAMPO_4$), and pyridoxic acid (PIC) from the sample and their identification by their fluorescence characteristics under selected pH conditions. Fig. 1 shows the typical group of curves obtained for the whole blood content of (1) pyridoxal phosphate, (2) pyridoxamine phosphate, and (3) pyridoxic acid. Since the pyridoxine form of B_6 is rapidly converted into pyridoxal phosphate and pyridoxamine phosphate by the body, this technique makes possible the

measurement of these physiologically active forms in blood and urine.

In this study, 220 normal pregnancies were followed at monthly intervals to term. Alternate patients were distributed between two groups. One group of 99 controls received no vitamin B_6 and 121 patients were given 6 mg. of pyridoxine daily.

Results and comment

Fig. 2 illustrates a summary of our observations on pyridoxal phosphate, pyridoxamine phosphate, and pyridoxic acid levels in blood during normal pregnancy, without any supplementation with vitamin B_6. As can be seen, the early prenatal patient exhibited a range of vitamin B_6 ($PALPO_4$ and $PAMPO_4$) in the blood comparable to that of the nonpregnant woman. In the first month there was little alteration unless the patient had a smaller than normal dietary intake of B_6. By the end of the second to the third month, there began a progressive decrease in pyridoxamine phosphate. From the fourth to the fifth month the level fell appreciably. Although the pyridoxamine level declined, the pyridoxal phosphate level was maintained within a reasonably constant range and increased to double the initial values between the third and fifth months. Simultaneously, from this point on, the patients maintained blood levels in this range or showed slow continued decreases in values to term. The pyridoxic acid formation increased to some extent at the third to fifth month, followed by a gradual decrease during the last half of pregnancy. Table I quantitates the fluorescence values in our system for this group for pyridoxal phosphate, pyridoxamine phosphate, and pyridoxic acid in terms of millimicromols per milliliter. In view of the fact that the great bulk of the blood B_6 is pyridoxamine, the striking feature of these observations is that, although they confirm the current concept of low blood levels of B_6, they reveal a significant increase in pyridoxal which is masked by the total values.

The urinary excretion of pyridoxal phosphate, pyridoxamine phosphate, and pyri-

Table I. Whole blood values obtained for $PALPO_4$, $PAMPO_4$, and PIC throughout pregnancy for normal controls did not receive supplementary vitamin B_6

Months gestation	*$PALPO_4$ (mμM/ml.)*	*$PAMPO_4$ (mμM/ml.)*	*PIC (mμM/ml.)*
1- 2	0.052 ± 0.017	1.37 ± 0.12	0.369 ± 0.120
2- 3	0.092 ± 0.011	1.13 ± 0.15	0.477 ± 0.151
3- 4	0.112 ± 0.040	0.72 ± 0.14	0.504 ± 0.108
4- 5	0.100 ± 0.044	0.57 ± 0.17	0.306 ± 0.144
5- 6	0.044 ± 0.024	0.48 ± 0.20	0.228 ± 0.124
6- 7	0.052 ± 0.028	0.45 ± 0.23	0.227 ± 0.107
7- 8	0.048 ± 0.021	0.39 ± 0.11	0.175 ± 0.036
8-10	0.044 ± 0.020	0.32 ± 0.14	0.256 ± 0.126

Table II. Whole blood values obtained for $PALPO_4$, $PAMPO_4$, and PIC throughout pregnancy for normal patients receiving 6 mg. of supplementary vitamin B_6 daily

Months gestation	*$PALPO_4$ (mμM/ml.)*	*$PAMPO_4$ (mμM/ml.)*	*PIC (mμM/ml.)*
1- 2	0.076 ± 0.024	1.64 ± 0.54	0.427 ± 0.086
2- 3	0.116 ± 0.036	1.39 ± 0.32	0.472 ± 0.049
3- 4	0.128 ± 0.037	1.12 ± 0.13	0.517 ± 0.055
4- 5	0.104 ± 0.040	0.66 ± 0.21	0.328 ± 0.045
5- 6	0.083 ± 0.024	0.71 ± 0.20	0.404 ± 0.132
6- 7	0.084 ± 0.039	0.89 ± 0.24	0.556 ± 0.066
7- 8	0.080 ± 0.037	1.08 ± 0.23	0.639 ± 0.103
8-10	0.072 ± 0.031	1.40 ± 0.26	0.730 ± 0.217

doxic acid paralleled the picture seen in the blood.

At term, pyridoxamine values were at a low point with a slight trend to increase. However, within 24 hours after delivery, there was a rapid shift toward normal, reaching the prepartum range within the next 3 to 4 days.

Our findings on premature infants delivered after 6 months of gestation show them to have relatively high blood levels of B_6. However, tests obtained 24 hours after delivery on the full-term newborn infants show low levels similar to those found in the mothers. Previous studies on cord blood by Glendening, Wachstein, and Chow, have shown that the infant is amply supplied with pyridoxal phosphate at the expense of the mother.[13, 14, 20] This is apparently a transient phenomenon and following delivery the infant must depend upon his own diet for vitamin B_6. This is an interesting corollary to previous reports describing the early appearance of central nervous system abnormalities in infants who have not received adequate dietary B_6 or who have an abnormally high requirement for this vitamin.[21, 22]

Fig. 3 summarizes our findings in patients receiving 6 mg. of vitamin B_6 throughout pregnancy. As can be seen, there was no difference between this group and the controls during the first 6 months of pregnancy. Again there was an increase in pyridoxal phosphate with a coincidental fall in pyridoxamine phosphate during the first 3 to 5 months. The same rise in pyridoxic acid occurred during the middle trimester. It is only in the third trimester that a difference appears.

In Table II are presented the values for pyridoxal phosphate, pyridoxamine phosphate, and pyridoxic acid that were found in this group. However, despite this relative increase in vitamin B_6, we found from other unpublished data on amino acid changes during this period that an appreciable percentage of these women did not show correction of intracellular B_6 needs. We therefore feel that the daily intake of 6 mg. was not adequate and have expanded this study to include dosages up to 15 to 20 mg. daily.

The urinary excretion of pyridoxal phosphate, pyridoxamine phosphate, and pyridoxic acid were also elevated compared with controls. The blood and urine levels at term were higher than in the controls, and the postpartum return to prepartum values was accelerated. Furthermore, the infants of treated mothers showed higher B_6 blood levels 24 hours after delivery.

It is interesting to note that the vitamin B_6 changes with marked decrease in pyridoxamine phosphate and increased pyridoxal phosphate during the first half of pregnancy coincide with the tremendous physiologic alterations taking place in mother and fetus. The embryo during this period increases a billion times in size with prodigious requirements for protein formation and cellular growth, particularly of the central nervous system. These geometric increases in needs of the fetus must be met by extracting vitamin B_6 through the placenta from the mother, producing a relative deficiency in her. This is reflected in the fall in the pyridoxamine level. The pyridoxamine phosphate appears to serve as a reservoir from which pyridoxal phosphate is drawn so that the coenzyme is maintained at a constant concentration. While this may represent a "normal change for pregnancy," the B_6 depletion may cause inhibition of intracellular enzyme systems with resultant pathologic changes. This situation may be further aggravated in the pregnant woman who has had poor dietary intake prior to or during the first trimester, resulting in a marked reduction of the stores of pyridoxamine phosphate. She could then be subject to more severe complications of pregnancy in addition to possibly endangering the normal development of the fetus.

Data at hand along with unpublished information on amino acid degradation show that quadrupling the intake by daily supplementation with 6 mg. of vitamin B_6 is not adequate to alter this pattern. Additional studies now in progress suggest that the daily intake must be increased to 15 to 20 mg. to

produce any effect on blood levels and stores of pyridoxamine in the first 6 months. This is of particular interest since the majority of preparations in common use for prenatal care do not supply this amount when taken in their recommended dosages.

Summary

By means of the spectrophotofluorometric procedure, all of the members of the vitamin B_6 group were measured in both blood and urine during the course of 220 normal pregnancies.

One group of 121 patients were given 6 mg. of pyridoxine daily and 99 controls received no vitamin B_6.

In the first month there was little alteration in the two groups, but by the end of second and third months a progressive decrease in pyridoxamine phosphate occurred, followed by an appreciable fall in the second trimester. Throughout gestation, pyridoxal phosphate levels were relatively stable with an increase at the third to the fifth month.

The urinary excretion paralleled the blood picture changes.

Premature infants had relatively high blood levels of B_6, but full-term newborn babies showed low levels similar to those in the mothers. Infants of treated mothers showed higher B_6 blood levels 24 hours after delivery.

Maternal intracellular stores may be depleted with resultant pathologic changes, and this may be further aggravated in the pregnant woman with a poor dietary intake of B_6 prior to pregnancy.

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The cardiac output changes in various positions in pregnancy

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THE objective of this study is primarily to study the effect of position in cardiac output during pregnancy. To understand the cause of cardiac output change induced by position, we must consider other hemodynamic changes which occur secondarily to position. Waterfield[1] found the blood volume to be diminished in the vertical compared to the recumbent position. This loss was mainly in the plasma fraction and amounted to a 15 per cent decrease in the total plasma volume. The above results correspond very well to the findings of Perera and Berliner[2] on the hemoconcentration found in the standing position. They also found a rise in the serum proteins when the standing position was assumed. The above decrement of blood volume in the vertical position helps explain the diminished cardiac output in the erect position. The decreased volume in the erect position leads to a decrease in the diastolic filling volume and subsequently a diminished cardiac output. A decrease in cardiac output in man on changing from the recumbent to the standing position was reported by Lindhard,[3] McMichael,[4] and Bazett and associates.[5] McMichael and Sharpey-Schafer[6] found a difference in cardiac output between the recumbent position and the standing position. The average cardiac output by the Fick method in the supine position is 5.3 L. per minute, while in the standing position it is 25 per cent less, or 4.0 L. per minute.

Stead and Ebert[7] and Hickam and Pryor[8] have studied the alteration of all these hemodynamic factors in motionless standing. It is believed the normal response to a fall in blood pressure is fundamental to the production of postural hypotension. It is then apparent that significant postural hypotension can occur without a greater than normal fall in cardiac output. It is also possible to have a large significant fall in cardiac output without a concomitant fall in blood pressure. However, large pressure drops may be associated with large drops in cardiac output. It is presumed that these large falls in output result from an inadequate venous return to the heart. An apparent cause of decreasing venous return is an abnormal dilatation of the venous system under increased hydrostatic pressure. Normally, the venous system resists passive dilatation under hydrostatic pressure in the upright position and venous return is well maintained. Active venous constriction is a familiar response to circulatory inadequacy as in shock and congestive failure. It is quite possible that an increase in venous tone is an important normal response to assuming the upright position. Hickam and Pryor's[8] results suggest that "such a response would assist in main-

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taining the cardiac output, just as arteriolar constriction maintains the blood pressure."

McLennan and Thouin[9] studied the average course of antecubital and femoral venous pressure throughout normal pregnancy and the immediate puerperium. He found in 30 normal nonpregnant women the average antecubital venous pressure in the supine posture was 7.88 ± 0.31 cm. of water and the average femoral venous pressure was 11.43 ± 0.64 cm. of water. Antecubital venous pressure in normal pregnancy is not significantly different from that in nonpregnant state. Femoral venous pressure in normal pregnancy, however, begins to rise in the early part of the second trimester, rises rather rapidly between the twentieth and thirtieth weeks of gestation, then somewhat more slowly reaches an average peak value at term of approximately 24 cm. of water. It falls quickly after delivery to nonpregnancy levels and apparently lies somewhat below the average control level during the puerperal period of bed rest. This work demonstrates that some hindrance exists in venous return from the lower extremities or possibly from the entire lower half of the body.

Howard, Goodson, and Mengert[10] wrote on the supine hypotensive syndrome. They found that compression of the vena cava by the flaccid, near term, pregnant uterus is the etiological factor in the "supine shock syndrome." This occurs only late in pregnancy and is relieved by assumption of any posture except supine. The phenomenon does not develop instantaneously since it depends upon pooling of blood in the lower extremities with subsequent depletion of blood from the heart and lungs. They noted that in the mid-dorsal region the anterior surface of the vertebral column is at least 3 cm. anterior to the most posterior portion of the peritoneal cavity. Thus, the relatively soft vena cava is protected from pressure during a labor contraction by the long vertebral column when the patient is supine. On the other hand, the flaccid uterus may often bulge posteriorly on either side of the vertebral column and compress the cava. The aorta does not suffer because there is a relatively higher pressure within it than in the inferior vena cava; also, it is thicker walled. They found this shock syndrome present in only 11 per cent of the patients examined and felt the variation of individual anatomic configuration and degree of flaccidity of the pregnant uterus accounted for this.

The main thesis of the experimental data to be presented is concerned with postural changes and their relationships to the cardiac output at the time of delivery. The ultimate aim is that the results may be of some aid in the treatment of certain cardiovascular disturbances concomitant with or as a direct result of pregnancy.

Methods and materials

The observations were made on 31 normal pregnant women in the last lunar month of pregnancy. They were a mixture of primigravidas and multigravidas, Caucasians and Negroes. They had hemoglobin levels of 10 Gm. per cent or above, and weighed less than 150 pounds. A ½ to 1 hour resting period in bed was permitted in order for the patients to become acclimated to their surroundings and to reduce any anxiety.

The brachial artery was then located by palpation and the skin and periarterial area were infiltrated with a 1 per cent lidocaine solution for local anesthesia. A thin-walled 18 gauge Cournand needle was then placed and threaded into the artery without much difficulty in the majority of instances. In the other arm a large-sized vein was sought; for this, an antecubital vein was most frequently utilized. After administration of 1 per cent lidocaine solution, a thin-walled 14 gauge short bevel venous needle was inserted through which a sterile catheter was threaded. The catheter was 0.065 inches in diameter, and was of such length (50 cm.) that it was able to lie within the thoracic cage, but not in the right atrium. This, therefore, prevented any error from a possible Valsalva maneuver and also permitted the dye to be delivered to the circulation in a single large wave.

After the arterial Cournand needle and

venous catheter were checked for correct positioning and patency, the Lucite collecting discs were heparinized. The disc was then placed on a constant-speed electric motor sample collector which rotated at 60 cuvettes per minute. The collecting device was a modification of that of Rothe and Sapirstein.[11]

Sulfobromophthalein sodium is confined to the plasma and has the advantage of being rapidly eliminated from the blood by the reticuloendothelial system, particularly by the Kupffer cells, from these gradually into the polygonal cells of the liver, and then excreted in the bile.[12] The use of this dye, after a modification of Wassen,[13] facilitated the determination of serial outputs within short time periods. The dye is also nontoxic, nonallergenic, and colorless in neutral solutions, as blood. After the thin-walled 18 gauge Cournand needle was attached to the collecting disc by means of a polyethylene catheter of 2 mm. diameter and adequate arterial flow was obtained, 2 ml. of a 50 mg. per milliliter sulfobromophthalein sodium solution was rapidly injected via a 2 ml. syringe with a hub needle connected to the venous catheter. The injection was made as rapidly as possible. Arterial samples were collected in the rotating inset cuvettes for a period of 30 seconds. At this time, the polyethylene delivery tube was disconnected from the Cournand needle and replaced by a blunt-end stylet. The venous catheter was rinsed with 25 ml. of normal saline to rid the catheter of residual dye. An elimination period for the dye and an equilibration period for the patient totaled 15 minutes before a subsequent determination was accomplished. The amount of blood loss per determination approximated 15 to 20 ml.

One half milliliter aliquots of whole, heparinized blood were pipetted from the individual inset cuvettes into 5 ml. of isotonic saline. The samples were centrifuged for 10 minutes at 3,000 r.p.m. The supernatants were transferred to Wassermann tubes. The dye was brought out just prior to reading by the addition of 1 drop of concentrated sodium hydroxide to each sample, in order

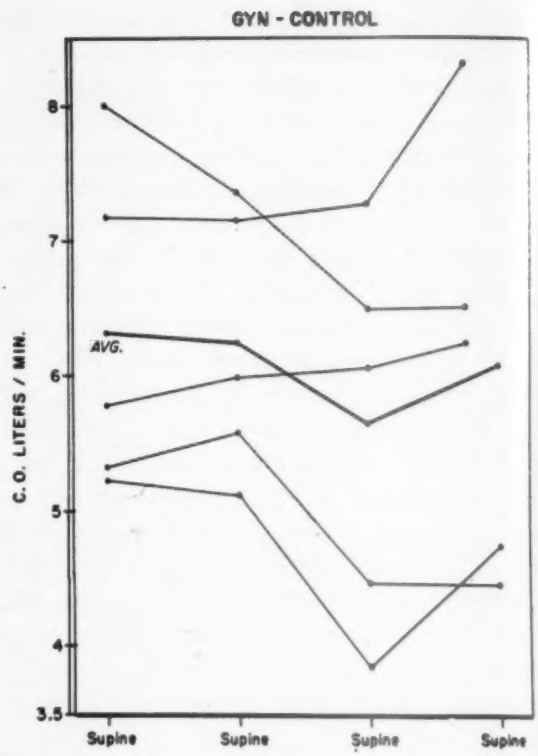


Fig. 1

to create an alkaline solution. Samples were read in a Beckman DU spectrophotometer against a blank of similarly diluted dye-free blood. A standard was prepared by injecting 2 ml. of dye through the identical catheter and syringe used in the study (so the dead space is the same) into a 1 L. volumetric flask and diluting to 1 L. with isotonic saline. A 0.5 ml. aliquot of diluted standard was added to 4.5 ml. of isotonic saline plus 0.5 ml. of blank dye-free blood in order that the medium for the standard would be the same as for the other samples. All readings were accomplished at a wave length of 565 μ where sulfobromophthalein sodium exhibits maximal absorption.

No hematocrit corrections were necessary as the use of whole blood in the manner described provides the whole blood output.

The readings, after subtraction of the blank reading, were plotted on 2 cycle semilogarithmic paper. The peak of the curve was obtained within 3 to 4 samples after the appearance of the dye. The descending limb was determined by at least 5 or 6 points be-

fore recirculation occurred. The most appropriate straight descending line was drawn connecting the points and extrapolated to zero. The points were added. The extrapolated portion was accomplished by determining the slope of the descending limb. if we let r equal slope, P_1 equal the last point added, and P_2 equal the following point not added to the total, the formula is $r = \frac{P_2}{P_1}$. Thus, r was used in calculating the extrapolated area by the formula: Extrapolated area $\frac{P_2}{1-r}$. The previously added points up to the extrapolated area were added to the extrapolated area to give the total area under the curve.

To determine the cardiac output, the following formula was used.

$$\text{Output} = \frac{\text{Standard} \times 1000 \times 60}{\text{Total area}}$$

where the blank corrected standard multiplied times its dilution (1,000 ml.), times the velocity of the rotating disc (60 samples per minute), divided by the total area afforded an accurate determination of cardiac output.

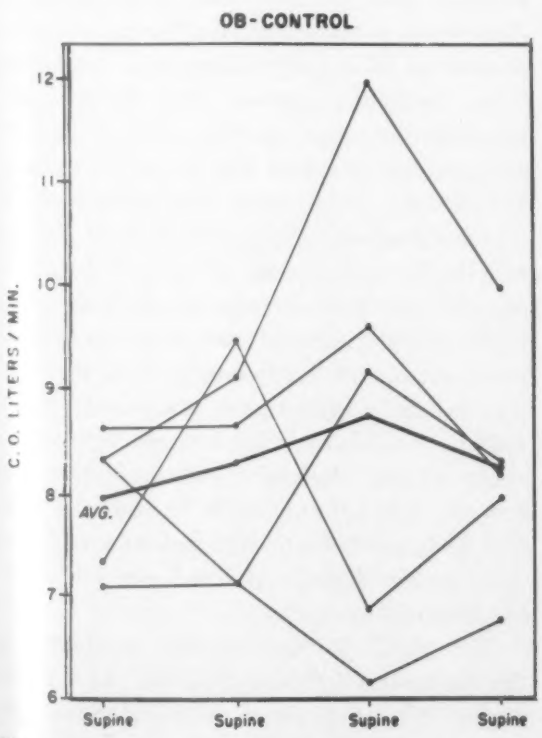


Fig. 2

Results

A total of 125 cardiac output values were calculated in the following various positions. In order to determine control values by the above method, 20 cardiac output determinations were accomplished on 5 normal nonpregnant women in the supine position. The average cardiac output was 6.06 L. per minute. As the following graphs will demonstrate, a small inconstant variation occurred between the 4 cardiac output values per individual. In addition, when the totals of all the first, second, third, and fourth determinations in the supine position were averaged and plotted, an insignificant difference was noted which ranged between 5.65 and 6.30 L. per minute (Table I and Fig. 1).

To further compare experimental data to controls, a second series identical with the above except that the female subjects were in the last month of pregnancy was carried out. The mean cardiac output for this obstetric series was 8.29 L. per minute. This was 2.23 L. per minute above the nonpregnancy values obtained. The variation of the totaled first, second, third, and fourth supine values averaged and plotted also demonstrate only a slight difference. This variation ranged between 7.94 and 8.74 L. per minute (Table II and Fig. 2). These aforementioned results lead to the conclusion that the amount of blood lost during output determinations is negligible as far as affecting the results obtained. The amount of blood lost totaled 60 ml. However, the controls do show a slight spontaneous variation without changing the experimental conditions.

When we consider the cardiac output of the gynecologic control patient and the obstetric control patient, a difference is noted. If we examine the definition of an obstetric control patient, it is noticed that 50 of the determinations fit the criteria. The average cardiac output value of these 50 supine pregnant women at term is 7.51 L. per minute. This represents a 1.45 L. per minute increase of the supine term obstetric patient over the nongravid control. This represents a 23 per cent increase in cardiac output, consistent with the existing literature.

Table I. Gynecologic controls (values in liters per minute)*

Patient	*Supine*	*Supine*	*Supine*	*Supine*
1	5.33	5.57	4.45	4.42
2	5.24	5.14	3.91	4.72
3	8.00	7.35	6.60	6.64
4	5.78	5.98	6.04	6.22
5	7.16	7.13	7.25	8.29
Total	31.51	31.17	28.25	30.29
Average	6.30	6.23	5.65	6.06

*Standard deviation, 0.278; mean 6.06.

Table II. Obstetric controls (values in liters per minute)*

Patient	*Supine*	*Supine*	*Supine*	*Supine*
1	8.32	7.11	6.16	6.75
2	7.09	7.11	9.15	8.28
3	8.62	8.64	9.59	8.16
4	8.32	9.10	11.95	9.94
5	7.33	9.46	6.87	7.93
Total	39.68	41.42	43.72	41.06
Average	7.94	8.28	8.74	8.21

*Mean of 5 obstetric controls, 8.29; mean of total obstetric controls (50 demonstrated), 7.51; standard deviation (5 obstetric controls), 1.042.

Table III. Lithotomy position (values in liters per minute)*

Patient	*Supine*	*Supine*	*Lithotomy*	*Supine*
1		5.37	5.62	6.64
2	5.34	5.00	4.89	5.02
3	7.24	7.55	4.34	6.20
4	6.52	6.01	5.82	7.72
5	6.94	6.99	6.32	7.65
Total	26.04	30.92	26.99	33.23
Average	6.51	6.18	5.40	6.65

*Average decrement in lithotomy position, 1.10; percentage decrease in lithotomy position, 16.92; standard deviation, 0.500.

Table IV. Walcher position (values in liters per minute)*

Patient	*Supine*	*Supine*	*Walcher*	*Supine*
1	5.02	5.71	4.91	4.87
2	5.37	5.94	4.81	5.97
3	8.98	7.99	6.49	6.56
4	5.26	5.65	5.45	5.22
5	7.44	6.84	6.92	6.66
Total	32.07	32.13	28.58	29.28

*Average decrement in Walcher position, 0.38; percentage decrease in Walcher position, 6.23; standard deviation, 0.420.

The next step was the evaluation of the lithotomy position and its effect on cardiac output. Twenty output determinations were accomplished, 4 per individual patient. For the establishment of a basal cardiac output for each particular patient, the first 2 determinations were in the supine position. The patient was then placed in the lithotomy position for another determination. The fourth determination once again was in the supine position. In all cases, the 2 output determinations in the supine position were relatively constant, whereas the cardiac output in the lithotomy position demonstrated a diminution. The following output in the supine position returned to previous levels. The average of the 9 cardiac outputs, supine, was 6.40 L. per minute; the following 5 output average, lithotomy, was 5.40 L. per minute; and the average 5 determinations, supine, was 6.65 L. per minute. This demonstrated a 1.10 L. decrement which is significant. The decrease in cardiac output in the lithotomy position varied between 0.23 and 2.10 L. per minute. The percentage of decrease was 16.92 (Table III and Fig. 3).

The evaluation of cardiac output in the Walcher position was then accomplished. This series is similar to the lithotomy series. A total of 20 output values were run, again 4 per individual patient. The initial 2 determinations were in the supine position. The patient assumed the Walcher position and another output was accomplished. The remaining output was in the supine. The 10 runs in the supine position averaged 6.22 L. per minute. The average of the 5 determinations in the Walcher position was 5.72 L. per minute, and the following 5 cardiac output values in the supine position averaged 5.86 L. per minute. The cardiac output decrease in the Walcher position amounts to 0.51 L. per minute with a range of 0.06 to 1.35 L. per minute. The percentage decrement in the Walcher position was 8.18 (Table IV and Fig. 4).

The third position studied was that of the horizontal left side position. This series totaled 26 output values in 6 individual patients. Two patients had 5 determinations,

whereas the other patients had 4. Beginning with the supine position, the series is alternated with the left side position as follows: the first, third, and fifth determinations were in the supine position, whereas the second and fourth were in the horizontal left side position. The average of 14 cardiac outputs in the supine position was 6.64 L. per minute and the average of 12 outputs in the left side position was 7.68 L. per minute. Therefore, an average increment of 1.04 L. per minute ranging between 0.75 to 1.48 L. per minute was noted when a patient changed positions from supine to horizontal left side. This amounted to a 13.54 per cent increase in output. The outputs increased in all cases where the patient changed from supine to a left side position (Table V and Fig. 5).

The remaining series was carried out to show if the Trendelenburg and the Trendelenburg left side positions would have any affect on the cardiac output. Twenty outputs were accomplished utilizing 5 patients. The 4 outputs per patient were run in the following positions: supine, Trendelenburg 45 degrees, Trendelenburg 45 degrees on the left side, and supine. In all 5 patients, there was a marked decrease in the cardiac output when the position was changed from supine to 45 degree Trendelenburg. This change was from an average of 8.43 L. per minute output in the supine position to an average of 6.89 L. per minute in the 45 degree Trendelenburg position which was a decrease of 1.54 L. per minute (18.27 per cent) in the cardiac output. However, with the patient remaining in the Trendelenburg inclination, but assuming a left side position, the output increased 1.02 L. per minute (from 6.89 to 7.91 L. per minute), a 12.90 per cent increase, corroborating the above results obtained in the left side position. When the patient reassumed the supine position from the left side 45 degree Trendelenburg, a subsequent decrement in cardiac output resulted. The change was from 7.91 L. per minute in the left side 45 degree Trendelenburg position to 6.79 L. per minute in the supine position. This decrement,

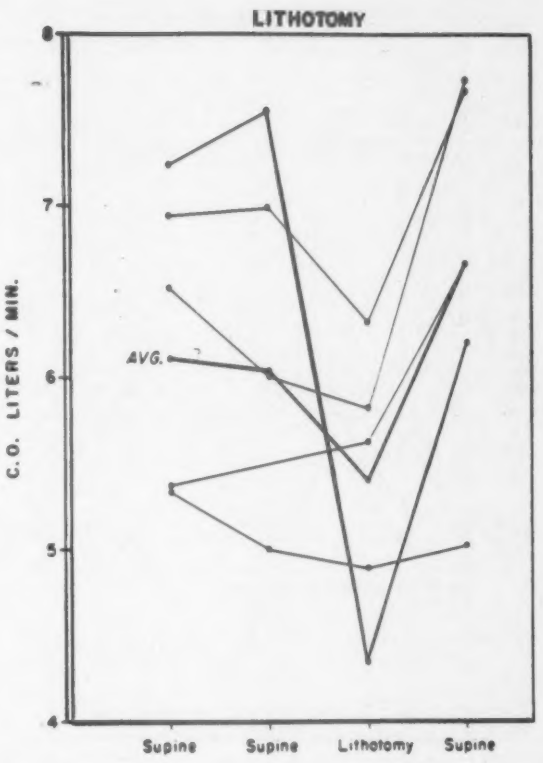


Fig. 3

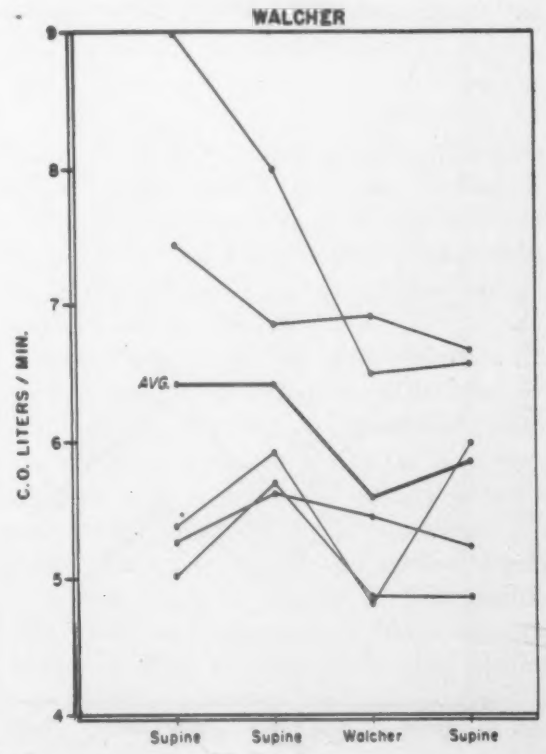


Fig. 4

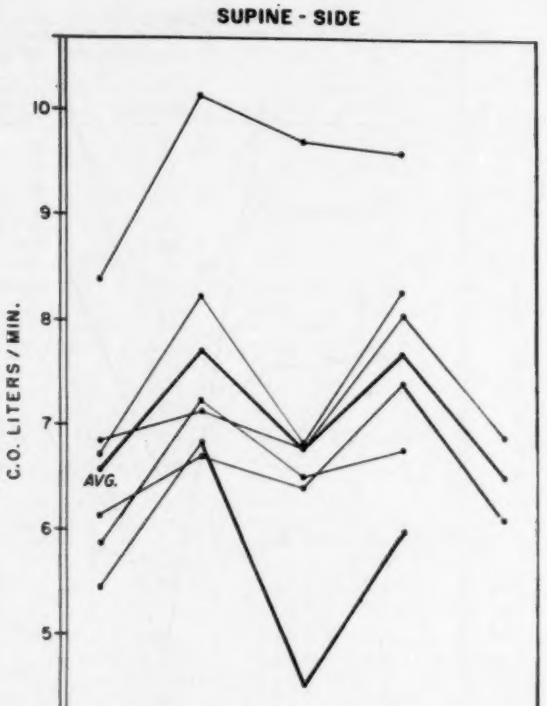


Fig. 5

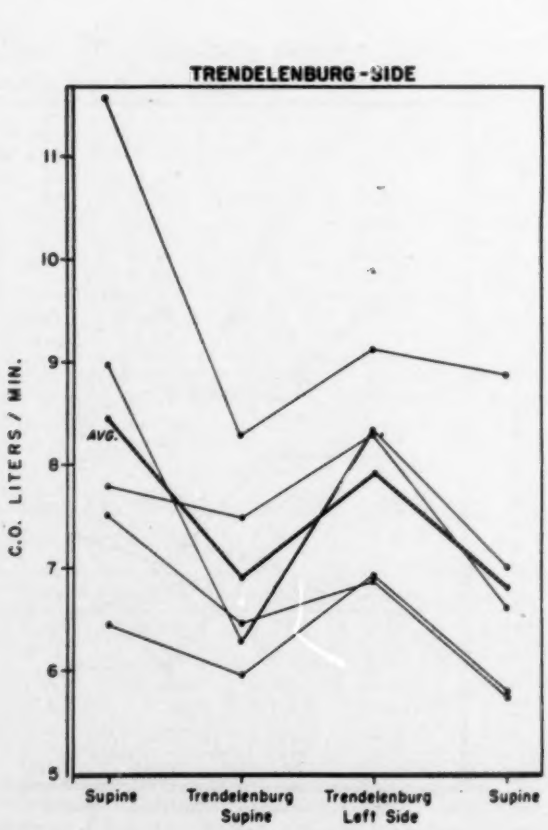


Fig. 6

therefore, amounted to 1.12 L. per minute, which was a 14.17 per cent decrease (Table VI and Fig. 6).

Comment

There are certain well-documented factors that affect cardiac output value. The most notable ones causing a decrease in the output are myxedema, congestive heart failure, and shock. The list of conditions that result in an increase in cardiac output value is more extensive. These vary from such physiologic factors as ingestion of food or fluids, exercise, and anxiety, to more serious causes as anemia, anoxia, febrile conditions, and thyrotoxicosis. One must bear in mind that cardiac output fluctuates with the pulse rate, the degree of diastolic filling, and the magnitude of the systolic discharge.

During pregnancy, the variation of cardiac output is primarily produced by an alteration in the degree of diastolic filling which, in turn, is dependent upon either the amount of venous return to the heart or the duration of diastole or both.

Most investigators consider that the rise of nearly 40 per cent in cardiac output and its subsequent fall toward normal near term in spite of a continued increase in plasma volume is probably best explained by the pooling of blood in the lower extremities and the consequent reduction in venous return to the heart.

By the findings of this report, it appears that certain positions either enhance or inhibit the pooling of blood in the lower extremities and, therefore, the diastolic filling which has its direct effect on the amount of cardiac output. By the results obtained, the flaccid uterus theory seems to be the primary agent in affecting the venous return; however, there may be other factors unknown at this time.

Although the experimental data do not include serial observations of cardiac output value throughout pregnancy, a very notable change is found in the amplitude of output increment during the last gestational month. When the cardiac output of the gynecologic group of 5 patients is compared with the

obstetric group, an increment is noted in the gestational patients. The 2 groups were identical in position utilized, both were supine. The increment that pregnancy exerts on the cardiac output in the last gestational month amounts to 23 per cent. It is evident, therefore, that pregnancy is associated with a marked physiologic elevation in cardiac output.

The series of patients in the lithotomy position demonstrate a decrease in cardiac output. The change in posture entails numerous readjustments of the circulation to gravitational effects. These various readjustments should have occurred within the 15 minute equilibration period; consequently, it can be accepted that the variation of cardiac output in the lithotomy position is justly correct. The difference in the cardiac output was always in the same direction. The conclusion resulting from the observation of a 16.92 per cent decrement in cardiac output in the above position might readily be expected when one realizes the effects of such a position on the "flaccid gravid uterus." It is easily visualized when a pregnant woman's lower extremities are tilted upward, as in the lithotomy position. The expected result should be an increase in output; however, in the above position the direction of force of the flaccid uterus is dorsal, enabling the flaccid uterus partially or totally to occlude the inferior vena cava. When this occurs, the venous return is reduced and a subsequent lowering of the cardiac output results. The change may be greater than that which is evident because of compensatory mechanisms exerting their influence.

The small decrement of the cardiac output, 8.18 per cent, in the Walcher position is in the direction of change that might be expected. When the lower extremities assume such a dependent position, one expects a pooling of the venous blood in the dependent part because of gravitational effects, which may become greater with a longer equilibration period. However, in this case, the maintenance of tone by the splanchnic area may prevent the accumulation of blood in those dependent regions where it would tend to gravitate. The variation is insignificant enough that one would be unable to derive any definitive conclusion as to the alteration of the cardiac output by the Walcher position.

If the above results of a decrease in cardiac output in either the lithotomy or the Walcher position are considered valid, this becomes useful information. It is well accepted that exercise and anxiety increase the output. Also, these 2 conditions are present in active labor. The patient exerts a marked degree of strenuous effort during labor and in many cases exhibits anxious moments. This is particularly true of the primigravida without medication. One is able to visualize very clearly that the elevated output can be diminished for such

Table V. Left side position (values in liters per minute)*

Patient	*Supine*	*Left side*	*Supine*	*Left side*	*Supine*
1	8.37	10.14	9.68	9.56	
2	5.87	7.21	6.49	6.73	
3	6.70	8.21	6.81	8.26	
4	5.45	6.82	4.51	5.95	
5	6.13	6.69	6.38	7.37	6.06
6	6.84	7.13	6.76	8.01	6.86
Total	39.36	46.20	40.63	45.88	12.96
Average	6.56	7.70	6.77	7.65	6.46

*Average increment in left side position, 1.04; percentage increment in left side position, 13.54; standard deviation, 0.2345.

Table VI. Trendelenburg back and left side*

Patient	*Supine*	*Trendelenburg back*	*Trendelenburg left side*	*Supine*
1	6.43	5.96	6.92	5.77
2	7.68	7.49	8.29	7.00
3	7.50	6.44	6.89	5.74
4	11.55	8.29	9.11	8.85
5	8.97	6.27	8.32	6.60
Total	42.13	34.45	39.53	33.96
Average	8.43	6.89	7.91	6.79

*Average decrement in Trendelenburg back position, 1.54; percentage decrease in Trendelenburg back position, 18.27; average increment in Trendelenburg left side position, 1.02; percentage increase in Trendelenburg left side position, 12.90; standard deviation, 0.4336.

a patient by the lithotomy or Walcher position during delivery. There is another condition, quite frequent during gestation, that may be aided by the positional effect, the "relative" anemia. As mentioned before, anemia causes an elevation in output. This is done in order to supply sufficient oxygen to the enlarging uterus and its contents. However, if the Walcher or lithotomy position were utilized and a lowering of the cardiac output occurred, the fetal hypoxia due to the already hemoglobin-poor blood and the deficient blood flow might be damaging enough to cause fetal distress.

In order to determine whether other positions have any influence on cardiac output, a modified left-sided Sims position was used. In a series of 12 outputs in the above position an average 13.54 per cent increase was obtained. When the left side position, is assumed, all the output determinations increased and approximated the above average. The knowledge of this positional increase in cardiac output becomes valuable especially as applied to patients with reduced cardiac output, as in myxedema, congestive heart failure, and shock, and also in obstetric conditions causing fetal distress, as abruptio placentae, placenta previa, and cord pressure, where any aid in maintaining an adequate uterine blood flow would be most advantageous. These data, therefore, have clinical application.

When the 45 degree Trendelenburg position is evaluated, findings similar to those of the lithotomy position were obtained. It is common practice to elevate the lower extremities of people in shock. This is believed to increase the venous return and by this means an increase in cardiac output is sought. The procedure of elevating the lower extremities is justified with the general population. However, by the experimental data, it can be stated that inclination of the body in the 45 degree Trendelenburg position would have the same consequence as elevating the lower extremities. The results show a depression of cardiac output when the Trendelenburg position is assumed. This amounts to a decrease of 18.27 per cent. Consequently, in any condition as mentioned previously, where the end results desired would be an increase in cardiac output, the Trendelenburg position is not warranted in full-term pregnancy. When the patient reassumed the left side position, while maintained in the 45 degree Trendelenburg inclination, the cardiac output value increased to the same extent as in the horizontal left side position; thus, it corroborates the increase in output found in the preceding horizontal left side position.

Conclusion

The positional effects on cardiac output have been reported (Tables I-VI and Figs. 1-6). The 5 positions most commonly used in the practice of obstetrics give the following results: increased: (1) horizontal left side 13.54 per cent, (2) Trendelenburg left side 12.89 per cent; decreased: (1) lithotomy 16.92 per cent, (2) Walcher 8.18 per cent, (3) Trendelenburg supine 18.26 per cent.

We are then presenting for consideration the fact that the horizontal left side and the Trendelenburg left side positions increase cardiac output and have certain clinical advantages. These positions are particularly effective when there is a need for elevation of cardiac output such as seen at the time of shock or fetal distress. In contrast, the lithotomy position and Trendelenburg supine position decrease cardiac output. We also feel the lithotomy position, following spinal anesthesia which stops active uterine contractions thereby prolonging the second stage of labor, is the cause of some fetal distress. We should like to make the point that if spinal anesthesia is given early the patient should not be placed in the lithotomy position until delivery is imminent, and that blood pressure is best maintained in this instance by the horizontal side position or acceptable vasopressors.

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Electroplating test patterns in pregnancy and the menstrual cycle

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IN A previous report,[1] an electroplating test for the detection of pregnancy was described. In this report it was suggested that the test method also might be employed to follow the course of pregnancy, to forewarn the onset of abortion, and perhaps to detect ovulation. In the present paper it is our purpose to report on the results of the electroplating test on urine obtained at regular intervals from 61 women during the course of pregnancy and from 19 women with regular menstrual cycles.

Methods

Collection of urine sample. All of the urine specimens were first morning samples, constituting between 8 to 12 hours of collection. The patients were instructed to abstain from food and liquids after midnight prior to when the urine sample was obtained. They also were advised to avoid, if possible, any medications for at least 24 hours prior to the test. Once the urine sample was obtained, it was refrigerated until the test was begun. In following the course of pregnancy, urine samples were obtained at least twice weekly, while in following the menstrual cycle they were obtained daily through at least two consecutive cycles.

Preparation of urine sample for the test. At the time of testing, a 10 ml. aliquot of the urine sample was acidified to a pH of 4.0 with 30 per cent hydrochloric acid and allowed to adjust to room temperature (between 20 and 25° C.). Following this, the urine was exposed to a charge of 12 volts direct current for 5.0 seconds in the electroplating unit as described in our previous report.

Interpretation of anodal plating. The superficial deposit was wiped from the surface and the anode was then placed in the photoelectric recorder which was adjusted to a microammeter reading of 5.0 from a standard coated anode. In following the course of pregnancy and the menstrual cycle, the numerical results were used simply to represent variations in the concentration of the urinary factors concerned with the test. During the course of pregnancy the plating test results tended to predominate above 3.5, while in the postpartum state and in the menstrual cycle they remained below this level.

Results

Course of pregnancy. The following cases represent typical electroplating test patterns obtained during the course of a full-term pregnancy.

Case 1—normal pregnancy. In Fig. 1, *A* the electroplating test results of daily urine specimens from Mrs. M. K. a 22-year-old gravida i, para 0, are recorded. She was about 4 weeks pregnant when first seen. At this time the electroplating test result was 2.25 (negative). Five

From St. Charles Hospital

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days later the rabbit test for pregnancy was positive. Following this the test results began to fluctuate between approximately 3.0 and 5.0. After 3 months of pregnancy they were in a lower range, between approximately 3.0 and 4.5. During the fifth month the test results had fallen to between 2.0 and 4.0. By the end of the eighth month the electroplating test results had risen to 5.0 followed by a progressive fall to 2.0 within one week. Following this they rose again to 5.0 within 10 days. During the next 48 hours they fell precipitously and the patient was delivered spontaneously of a full-term male infant. At the end of 72 hours after delivery the test results had fallen to 1.5 (negative).

In Fig. 1, *B* the average values of series of 10 consecutive electroplating test results of Mrs. M. K. have been plotted in order to accentuate the pattern obtained during a normal pregnancy. It is to be noted that the majority of the results in the first trimester fall within a range of 3.5 to 4.5, constituting what we refer to as a "high-titer" pregnancy. Further discussion of this classification will be presented later in this paper.

In Fig. 1, *C* the electroplating test results obtained during the postpartum period of Mrs. M. K. are depicted, along with those obtained in the ensuing second pregnancy. Notice that the majority of the electroplating test results fall well below the level of 3.5 during the postpartum period. However, at the estimated beginning of the patient's ensuing second pregnancy notice that the test results rapidly rise between 3.5 and 4.5.

In Fig. 1, *D* the average values obtained from series of 10 consecutive electroplating test results presented in Fig. 1, *C* are plotted in order to accentuate the pattern obtained in the postpartum state and ensuing second pregnancy.

Case 2—normal pregnancy. In Fig. 2, *A* the electroplating test results of urine specimens obtained from Mrs. B. H., a 35-year-old gravida v, para iv, are recorded. With this pregnancy the electroplating test at 4 weeks yielded a negative result of 1.6. Twelve days later she began to experience persistent nausea which increased in severity over the course of 5 days, being most severe on July 1, 1959, when the electroplating test result was 4.7. Two days after this the nausea had subsided completely and the electroplating test result had fallen to 2.6. For the following 3 days she was symptom-free. However, on the fourth day mild nausea recurred and persisted for 3 days. During this time the electroplating test result had risen to 2.9. At this point the nausea subsided and she remained symptom-free, the electroplating test result falling to 1.25. She then was about 2 months pregnant. During the third and ensuing months the test results fluctuated between 3.0 ad 4.5. After the beginning of the ninth month of pregnancy the electroplating test results rose to 4.4 and then began to recede somewhat. The patient then daily began to have mild uterine contractions for short periods of time. As the test results rose again to 4.65 these contractions increased in frequency. Following this the results fell precipitously during the next 48 hours and the patient was delivered of a full-term female infant. At the end of 72 hours the test result was 1.1 (negative).

In Fig. 2, *B* are recorded the test results of Mrs. B. H. obtained during the postpartum period and 4 consecutive ensuing menstrual cycles. Forty-eight hours after delivery she developed signs of urethrocystitis for which she received nitrofurantoin. Immediately, the test results rose to 5.0 from 2.0. Gradually they fell to lower levels. With the onset of menstrual cycles, the electroplating test results revealed a repetitive pattern that persisted below the level of 3.5. Further discussion of this pattern will be presented later in this paper.

Case 3—threatened abortion. In Fig. 3 are recorded the electroplating test results of Mrs. I. S., a 32-year-old gravida v, para ii. She had lost her last 2 pregnancies at 3 and 3½ months. When first seen she was about 3 months pregnant; the electroplating test result was 3.9 (positive) and the rabbit test was positive. In view of the clinical history the attending physician had given her 2.0 grains of desiccated thyroid daily during this time. As the pregnancy progressed, the electroplating test results tended to fluctuate between 3.5 and 5.0. At approximately 4½ months of pregnancy the electroplating test results began to fall rather sharply. After about 5 days of a continuing decline, the patient developed lower abdominal pains, perineal pressure sensations, and occipital headaches. Three days later the electroplating test result was 3.0. At this time the doctor gave her an additional grain of thyroid daily. Within 3 days the test result had risen to 3.25 (doubtful) and then after one week had attained a reading of 4.25 (positive). The test results then remained at this level for about 2 weeks. They then fell to 1.5 (negative) and the patient developed inter-

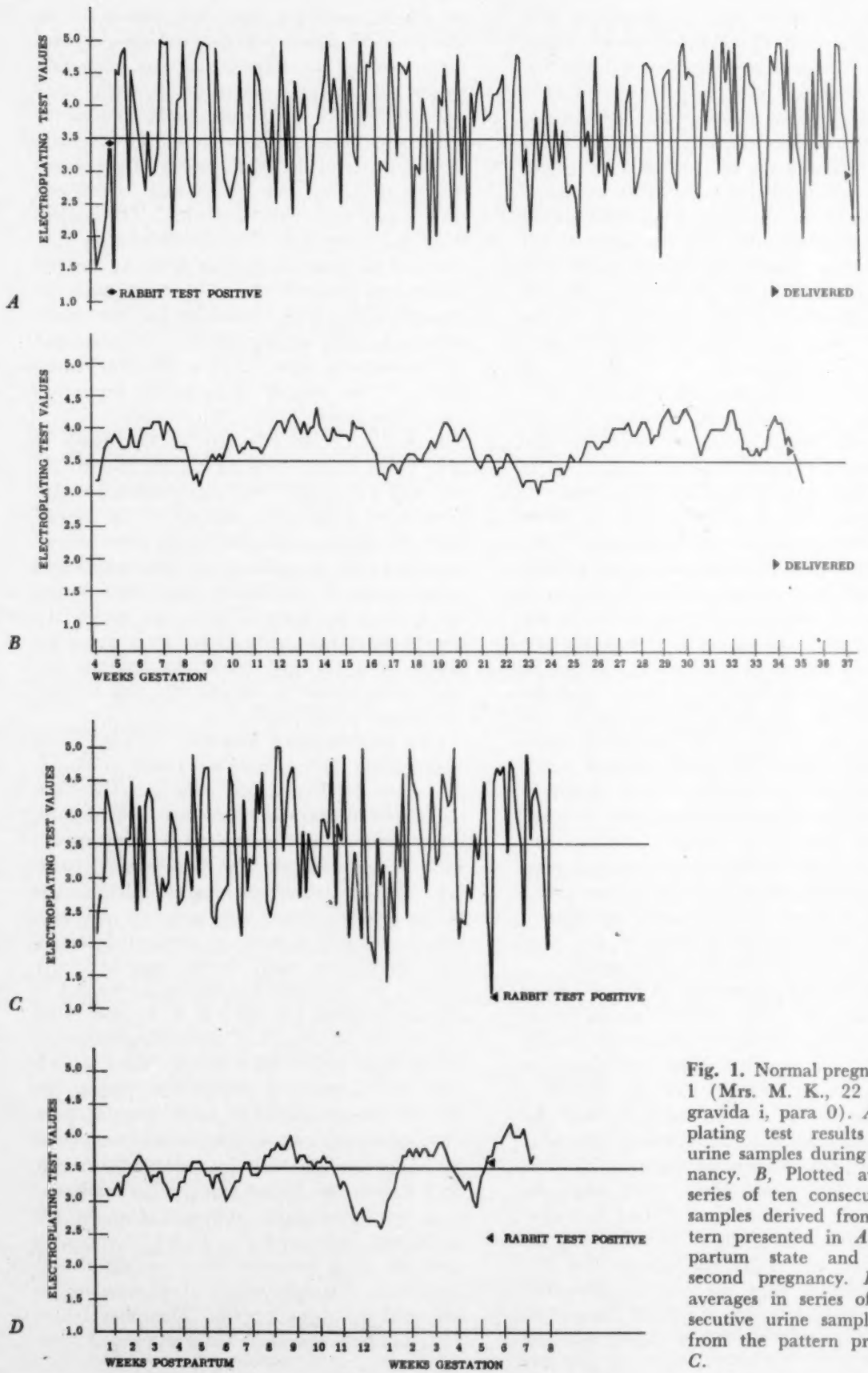


Fig. 1. Normal pregnancy, Case 1 (Mrs. M. K., 22 years old, gravida i, para 0). *A*, Electroplating test results of daily urine samples during first pregnancy. *B*, Plotted averages in series of ten consecutive urine samples derived from the pattern presented in *A*. *C*, Postpartum state and onset of second pregnancy. *D*, Plotted averages in series of ten consecutive urine samples derived from the pattern presented in *C*.

mittent headaches and soreness in the left gluteal region. Before the doctor could initiate any therapy the symptoms gradually subsided while the electroplating test results gradually rose to 4.0 (positive). She then was about 6 months pregnant. Gradually a slowly progressive decline in the levels of the test results was observed. With this she noticed an onset of progressive tiredness. At the end of the seventh month of pregnancy the electroplating test result fell to 2.7. She had no symptoms but the attending physician gave her an additional 1.0 grain of desiccated thyroid daily. The test results in the course of 2 weeks rose sharply to 4.2 but then gradually receded to 2.0. During the ninth month of pregnancy they rose gradually to 4.0. Five days after this she was delivered of a full-term baby girl; the electroplating test result at that time was 3.0. Unfortunately, no further urine samples were obtained.

Case 4—complete abortion. In Fig. 4 are the recorded electroplating test results of Mrs. M. T., a 29-year-old woman who had been married for 13 years but never had a proved pregnancy. In view of this the attending physician had placed her on 0.5 grain of thyroglobulin, daily for 6 months. When first seen by us she was about 2½ months pregnant. The electroplating test was 3.5 (positive) and the rabbit test was positive. However, after one week the electroplating test began to fall from 4.0, and at the end of 2 weeks had taken a sharp decline to a reading of 2.0 (negative). At that time the patient began to have vaginal spotting which persisted for 4 days. For 10 days the test result remained at this level and then the patient began to have uterine bleeding which grew worse progressively; this was accompanied by cramps. The rabbit test remained positive. The patient was given estrogen and progesterone and a combination of tridihexethyl chloride and meprobamate. The bleeding persisted and the patient passed portions of placental tissue in spite of additional treatment with lututrin. However the plating test results rose sharply to 4.45. Tweny-four hours after completion of the abortion the electroplating test was 1.0 (negative) and the frog test was negative but the rabbit test was positive.

Electroplating test patterns

Of interest are the electroplating test patterns obtained in menstrual cycles, various age groups, sexes and clinical states.

Menstrual cycle. Nineteen women were observed through daily electroplating tests of urine for at least 2 consecutive menstrual cycles. The studies completed constituted 48 cycles. The results obtained in 4 consecutive menstrual cycles of a 36-year-old woman are depicted in Fig. 5. Those obtained from a 16-year-old girl are depicted in Fig. 6. In Fig. 7 the electroplating test results obtained from a representative menstrual cycle are superimposed on the quantitative assays of hormone levels in the urine during an average menstrual cycle.

Age groups and sexes. In Figs. 8 and 9 are the electroplating test results obtained in various age groups and sexes. Some obviously approach a pattern similar to those obtained in the menstrual cycle. While it is strongly suggested in the 7- and 11-year-old girls (Fig. 8, *A* and *C*), it definitely in no way is suggested in the pattern of the 9-year-old (Fig. 8, *B*). The patterns obtained in the young boys (Figs. 9, *A*, *B*, and *C*) again gave some suggestion of those obtained in the menstrual cycles. However, in the adult male of 40 years (Fig. 9, *D*) no suggestion of the "menstrual cycle pattern" was obtained; nor could it be detected in 2 other adult males.

Post menopause. Mrs. H. H. H., a 65-year-old woman, was 15 years postmenopausal. In repeated studies no cyclic patterns could be detected (Fig. 10, *A*). The record of the test results represents a 30 day segment of these studies. This case is one of two studied. Both gave similar results.

Posthysterectomy. Mrs. K. D., a 33-year-old woman, had a total hysterectomy and bilateral salpingo-oophorectomy in 1953. The results of electroplating tests of the urine samples represent a 42-day segment (Fig. 10, *B*). During this time three major peaks were encountered. Clinically, no significant factor could be disclosed which might account for these. However, the patient did admit to a moderate intake of vodka and orange juice 24 hours before the first two peaks. In view of this she was asked to increase this intake. Following this, the third peak occurred. These results are stim-

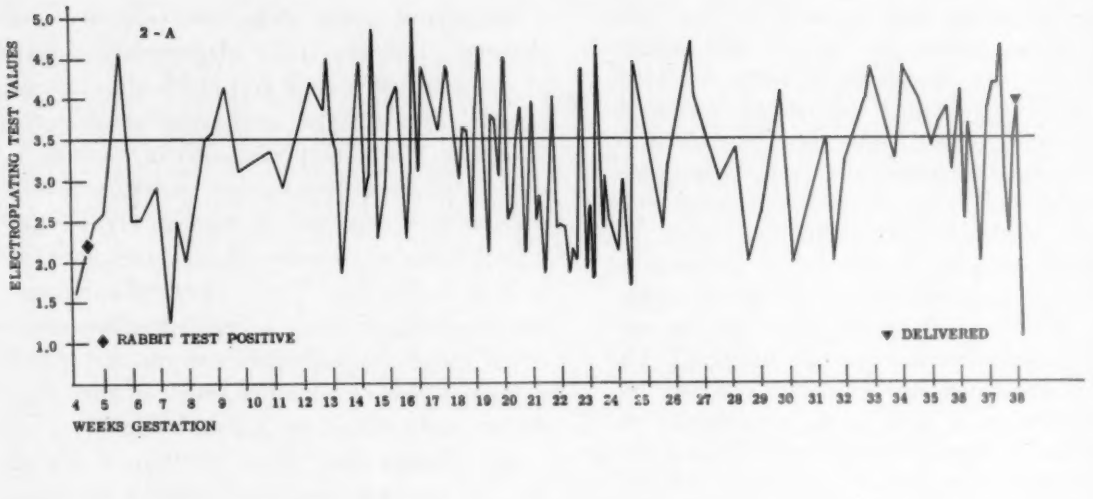


Fig. 2. Normal pregnancy, Case 2 (Mrs. B. H., 36 years old, gravida v, para IV). *A*, Electroplating test results of urine samples obtained during pregnancy. *B*, Test results obtained during postpartum state along with the repetitive pattern obtained during ensuing 4 menstrual cycles.

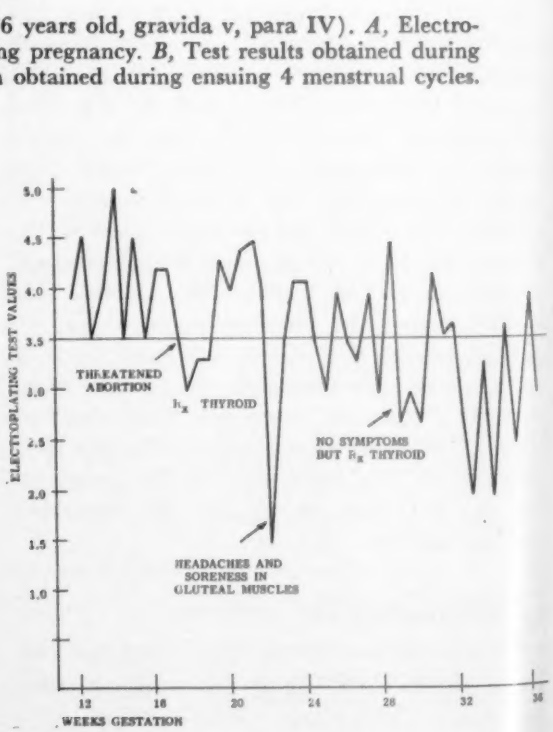


Fig. 3. Threatened abortion, Case 3 (Mrs. I. S., 32 years old, gravida v, para II). Electroplating test results of random urine samples obtained during the course of pregnancy.

ulating and suggest further studies, especially in view of a report by Sevag and Colton[2] concerning chemical determination of the ovulation time in women.

Comment

During the course of this study it became apparent that there are two levels of electroplating test results obtained during the first trimester of pregnancy. We have chosen to refer to these levels as "high titer" and "low titer" pregnancies. The former is characterized by results predominating over 3.5, while the latter is below this level. Further studies concerned with the classification of the pregnancy and its eventual outcome are being conducted since there appears to be a high incidence of abortion associated with the "low titer" pregnancy. Results of these studies will constitute a separate report.

In order to classify and follow the course of the pregnancy the patient should be at least 4 or, preferably, 6 weeks pregnant. Daily first morning urine samples should then be obtained for 2 weeks. These individual samples may be kept under refrigeration for one week before being tested. If the pregnancy is classified as "low titer," the patient should be followed closely clinically with daily electroplating tests and given proper medication as adjudged by the physician to preserve the pregnancy. Once she is classified as having a "high titer" pregnancy and being free of symptoms the physician need only test the urine twice weekly throughout the remainder of the pregnancy, unless the clinical status should warrant more frequent observations.

In regard to detecting the onset of a threatened abortion one must be aware of the precipitous falls in the results of the electroplating test which may occur in a 24 hour period. These should cause no immediate concern. However, a progressive fall over a period of several days, as seen in Figs. 3 and 4, demands the attention of the attending physician to the patient's clinical status. During the course of pregnancy the electroplating results tend to fall progressively after the fourth or fifth month,

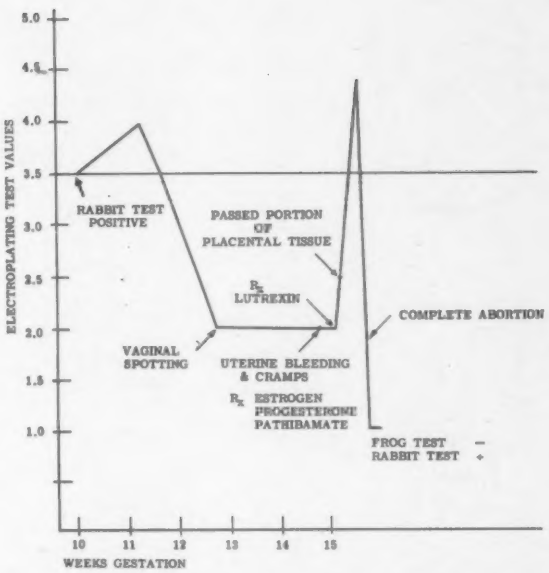


Fig. 4. Complete abortion, Case 4 (Mrs. M. T., 29 years old, married for 13 years but never had a proved pregnancy). Electroplating test results of random urine samples obtained during the course of pregnancy.

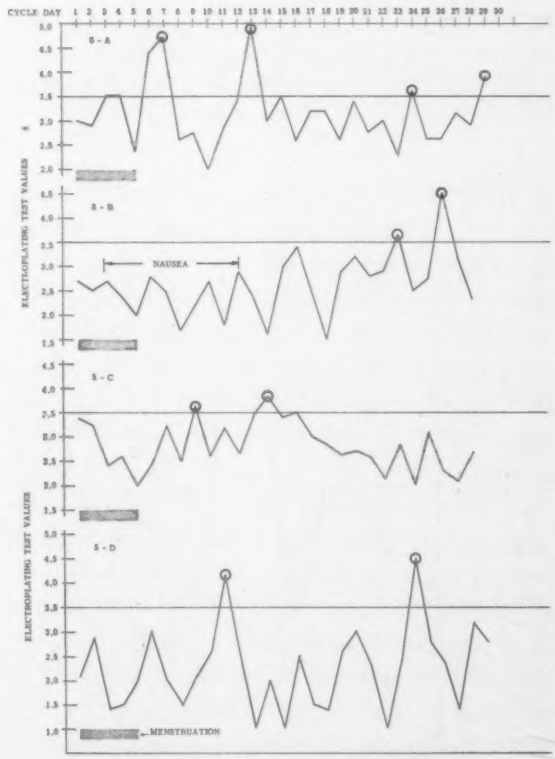


Fig. 5. Menstrual cycles, Case 2 (Mrs. B. H., 36 years old). First 4 consecutive menstrual cycles occurred after the delivery of the fifth child (Fig. 2, *B*). The encircled peaks represent "major peaks."

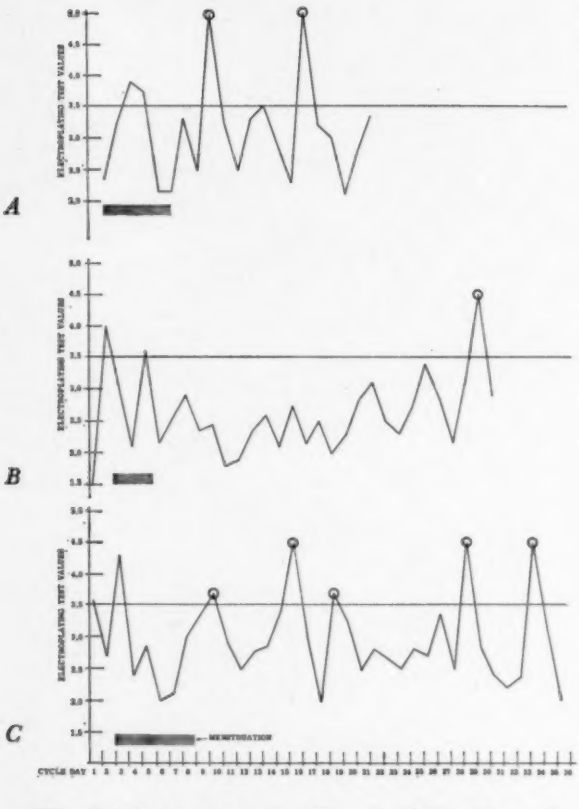


Fig. 6. Menstrual cycles, Case 6 (Miss M. A. K., 16 years old). Electroplating test results of 3 consecutive menstrual cycles. The encircled peaks represent "major peaks."

reaching the lowest point at the end of the eighth month. During the ninth month of pregnancy usually two peaks are reached; one at the beginning, and the other following this in 10 or 14 days. Usually, delivery will ensue within 3 days or one week after this.

Because of the patient's clinical state and her probable anxiety for the preservation of the pregnancy one should be judicious in his discussion of the test results with her. In our experience the women usually are relieved to know these results. One of our patients had severe episodes of varied symptoms during the course of pregnancy which, to her, caused great anxiety since she was gravida iv, para i, and Rh negative, her husband being Rh positive. On one occasion, during the fourth month of pregnancy she was admitted to the hospital because of vaginal spotting. The electroplating test results, however, remained at high levels. Knowledge of this relieved her anxiety. With additional treatment by the physician the symptoms subsided, and in a few days she was discharged to her home. At the time of this writing she is in the eighth month of preg-

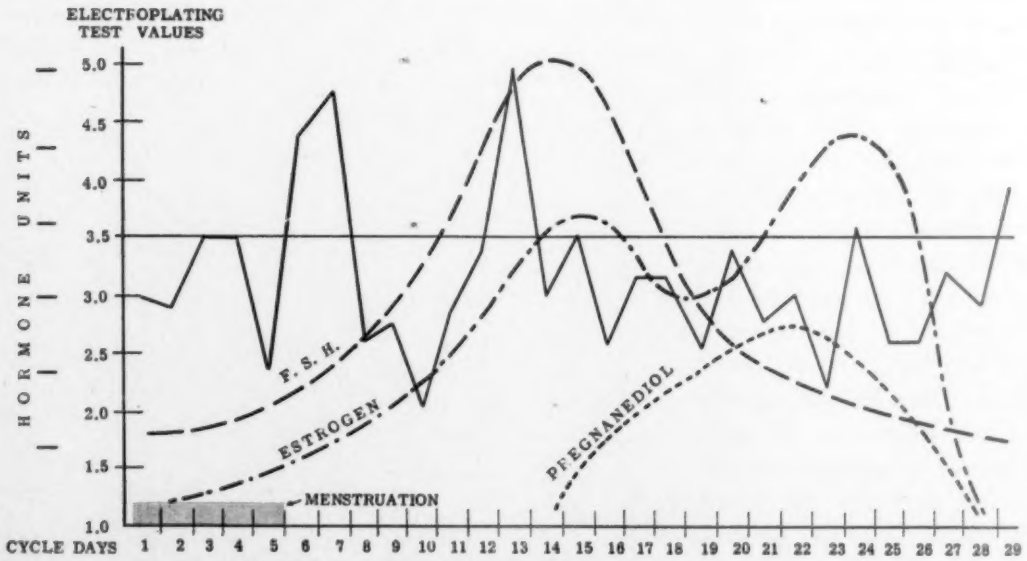


Fig. 7. Electroplating test results obtained from a representative menstrual cycle are superimposed on the plotted quantitative assays of hormone levels in the urine during an average menstrual cycle.

nancy, the electroplating test results are at proper levels, and she has had no further episodes of cramps or bleeding since the midportion of the fifth month of pregnancy.

The daily urine samples of the 19 women with regular menstrual periods showed that in most of the cycles the electroplating test results tended to rise progressively during the menstrual flow, reaching a peak and then receding to the approximate initial level. Following this a series of minor fluctuations developed which were interrupted by two, three, or more major peaks. The first of these major peaks usually occurred between the sixth and the tenth day, while the the second occurred between the eleventh and the nineteenth day of the menstrual cycle. The other major peaks usually occurred after the twenty-first day. This is clearly visualized in Figs. 5 and 6.

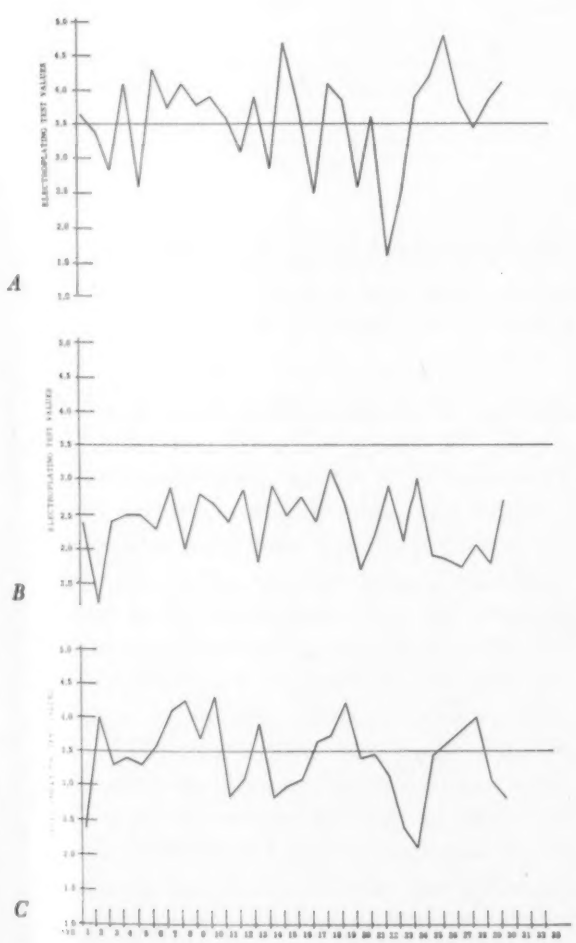


Fig. 8. Electroplating test results on urine obtained from adolescent females. *A*, 7 years old; *B*, 9 years old; *C*, 11 years old.

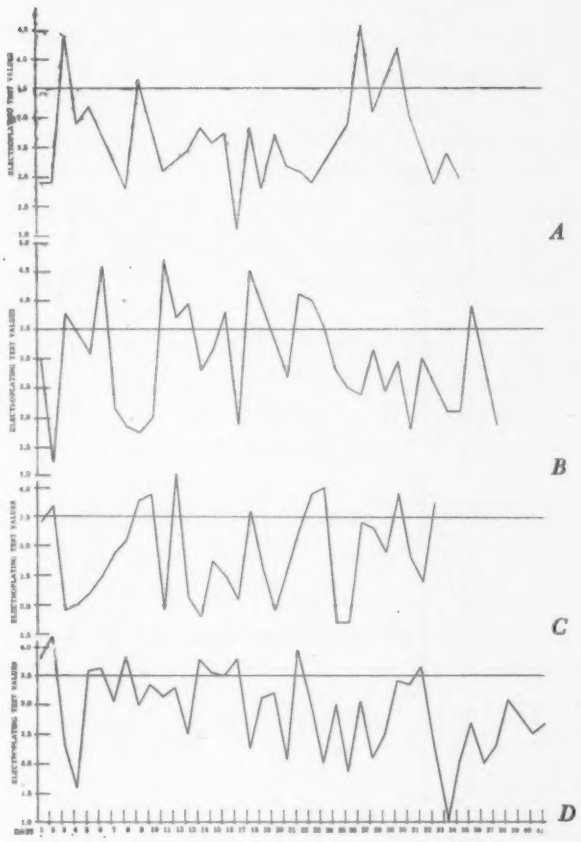


Fig. 9. Electroplating test results on urine obtained from males. *A*, 2 years old; *B*, 5 years old; *C*, 10 years old; *D*, 40 years old.

In view of these patterns the thought of one of the first two major peaks representing ovulation, and the lack of these peaks (see Figs. 5, *B* and 6, *B*) representing an anovulatory cycle, is intriguing. Because of this and the repetitive consistency of the patterns in menstrual cycles of the other women, further electroplating studies are being conducted with more clinical material in conjunction with other methods used for detecting ovulation. The results of these studies will be presented in a separate report.

Our experience with this test method has led us to conclude that it has its greatest clinical value in classifying and following the course of a pregnancy, detecting the onset of threatened abortion, measuring the effectiveness of treatment to prevent the abortion, and recording the termination of the

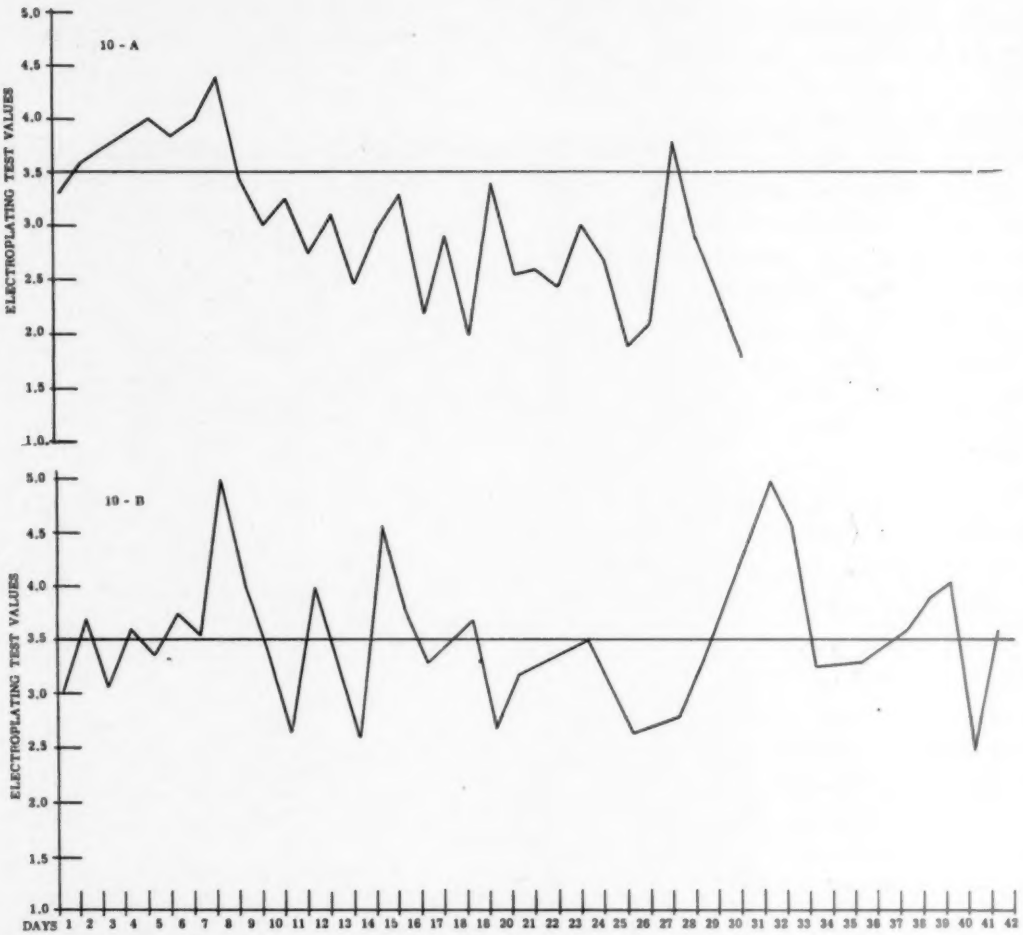


Fig. 10. Electroplating test results obtained on urine in various clinical states. *A*, 65-year-old woman, 15 years postmenopausal; *B*, 33-year-old woman, 7 years posthysterectomy.

pregnancy. In addition, present studies have led us to believe that with this test one may be able to predict the onset of labor. The exact nature of the substance or substances concerned with the test has not been ascertained. However, we feel that the test is measuring the concentration of a "biochemical complex," perhaps hormonal, through electroplating phenomena of the sulfate radical, which appears to be a sensitive indicator of the quality of the pregnancy state. Our determinations of the chemistry of this test method will constitute a separate report.

Summary

In a previous report[1] an electroplating test for the detection of pregnancy was described. The present paper constitutes a report of the electroplating test results of urine obtained at regular intervals from 61 women during the course of pregnancy and from 19 women with regular menstrual cycles.

All of the urine samples were first morning voided specimens and were refrigerated until the time of the test, when they were adjusted to room temperature and pH of 4.0. They were placed in the electroplating test unit and charged for 5 seconds with 12 volts direct current electricity applied through silver and copper electrodes. The silver anode became coated dull silver, gray, or black, or varying shades of these. The anode was then placed into a photoelectric recording unit and numerical microammeter values obtained, apparently corresponding to the variations in the concentration of urinary factors concerned with the test.

The results of these studies obtained dur-

ing the course of a full-term pregnancy, the postpartum period, and threatened and complete abortion are presented and discussed. In general, the test results preceded the onset of clinical signs of abortion by several days.

It is recommended that for classification of a high or low titer pregnancy a first morning sample of urine should be obtained daily for at least 2 weeks. In following the course of pregnancy at least two samples each week should be tested unless clinical signs or symptoms should prompt more frequent studies. The patterns obtained with these studies revealed a progressive decrease in the level of the test results after the fourth or fifth month of pregnancy, followed by a rather abrupt rise at the ninth month. Within 72 hours after delivery the test results fell sharply to negative levels.

From these studies it is apparent that the greatest value of the test method lies in classifying the pregnancy, following its course, and observing the response to the therapy the physician chooses for preserving the pregnancy.

Other studies of 19 women with regular menstrual cycles yielded patterns suggesting that the test method may be detecting ovulation. Further studies are being conducted to evaluate this.

Electroplating test patterns obtained in adult males, in children, and in women after menopause or hysterectomy are reported.

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Sparteine sulfate

A clinical evaluation of its use in the management of labor

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THE chemistry, toxicology, and pharmacology of sparteine sulfate has recently been reviewed in detail.[1] The drug undoubtedly has certain advantages over other oxytocic agents, the most outstanding of which are (1) that it can be administered intramuscularly, (2) that it does not require constant supervision, (3) that it may shorten the duration of labor, (4) that there are no known side effects, and (5) that it has a wide margin of safety. Its potential uses also encompass the postpartum period, an area which has received very little attention.

Numerous objective reports describe changes in frequency, duration, and intensity of contractions of the human uterus as a result of the administration of sparteine; there is unanimity of opinion on its efficacy. It is clear that in this sense sparteine sulfate has demonstrable oxytocic action, but isolated observations cannot be used to predict the effects of a large scale application.

Available reports are not suitable for statistical analysis. It seemed worthwhile, therefore, to design an investigation which would permit a statistical study of drug action and side effects, if any. The present report deals with such an evaluation where special attention was directed to the overall effect on the course of labor. It includes a sufficiently large number of patients to make the measurements statistically significant and to derive valid conclusions. The study was specifically designed to determine whether sparteine sulfate is of value to the practicing obstetrician or will remain merely a pharmacologic curiosity.

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Sparteine sulfate is supplied as Tocosamine by Trent Pharmaceuticals, Inc., New York, New York.

Intrapartum use

During the intrapartum period an oxytocic agent may be used for the induction and maintenance of labor, for producing more rapid progress in otherwise apparently normal labors, and for the treatment of abnormal dysfunctional states. The multiplicity of factors which together constitute labor makes it difficult to study each element of parturition individually. Their sum is reflected in cervical dilatation–time curves, which record the net result of all influences and provide bases for critical analyses.

Groups of patients that are identical in all details except for a single factor (such as the use of sparteine sulfate in one and omission of stimulation in another similarly constituted group) can be compared. Ideally, uniformity should exist among the groups which are to be contrasted, each being sufficiently large to permit the application of standard tests of significance. For the present study, it was necessary to accumulate over 1,000 treated patients in order to ex-

ceed the minimum needs for statistical purposes in each of several subgroups. A double-blind approach, although potentially more critical, was not possible under the conditions prevailing in this institution. Critical problems, often associated with the management of the parturient, contraindicate this manner of investigation because withholding of essential treatment may be detrimental to the health of the patient and the infant. As much information can be obtained and with considerably greater safety by the random use of the drug and subsequent retrospective interpretation of the data, mindful of course of underlying biases.

Patients. The patients used in this study were taken from the ward and private service of the Sloane Hospital for Women. Minimal restrictions on the use of the drug made it possible to obtain a representative cross section suitable for statistical comparison with existing unselected, untreated groups. Detailed analyses of these control groups have been reported.[2, 3]

Dosage. In preliminary trials, with 10 to 200 mg. of sparteine sulfate administered intramuscularly to normal nonpregnant patients, no effects on vital signs could be demonstrated or subjective symptoms elicited. The drug was made available to the professional staff of the obstetric service in 1 ml. ampules, each containing 150 mg. of sparteine sulfate. Although there were essentially no restrictions on the use of the drug, it was recommended that patients with active heart disease (digitalis-like effect of sparteine) and those with obstetric complications (cephalopelvic disproportion, uterine scars, placenta previa) be excluded. The drug could be used for the induction or stimulation of labor at the discretion of the attendant obstetrician. Although an interval of one hour between injections was recommended and adhered to in the large majority, in some instances the medication was repeated every 20 minutes without ill effects. The average number of doses for all treated patients in this series was 1.9 (range 1 to 11).

Procedure. The drug was administered in all phases of labor, a circumstance which eventually yielded information on drug effects under extreme circumstances. Cervical dilatation–time curves were constructed using the estimates noted in the patients' charts. All pertinent and relevant information derived from the charts together with that from the dilatation curves of the 1,364 patients who had received sparteine during the intrapartum period was then incorporated into a statistical analysis of the data.

Statistical evaluation. The distribution of variables such as maternal age, parity, gestational age, fetal weight, fetal position, type of delivery, and minor obstetric complications was essentially the same as that of our general obstetric population and of the controls.[2, 3] The groups compared in the subsequent discussion were thus identical except for one factor, the use of the oxytocic agent in one and not the other. In 89 of the 1,364 patients, the effect of sparteine sulfate was obscured by the concurrent or subsequent use of oxytocin. In 7, the observations were inadequate for an intelligent interpretation of the dilatation curves, and, in 60 failed inductions, no curves could be constructed. This left 1,208 patients with dilatation curves available for study in whom the progress of labor was influenced by the administration of the drug. In 183 of these, sparteine was administered before the onset of labor (for induction), in 849 during the first stage, and in 176 during the second stage. A further breakdown according to phases in the first stage is given in Table I, illustrating the random use of the drug.

Table I

Concurrent oxytocin administration	89	
Inadequate records	7	156
Therapeutic failures	60	
Drug administered		
For induction	183	
During first stage		
Latent phase	248	
Active phase	601	
During second stage	176	
For dysfunctional states	392	568
Total No. of "elective" patients		640
Total No. of patients		1,364

Unfortunately, only about half of all treated patients can be used for the specific study of drug effect, i.e., study of the influence of sparteine sulfate on the course of normal labor.

Because of its oxytocic characteristics, a natural tendency existed for the drug to be used largely in abnormal dysfunctional states or late in labor in order to bring about more rapid expulsion and delivery. Neither of these uses is suitable for the intended evaluation, and the exclusion of these patients would, it is hoped, clarify the issues.

In order to study the action of a drug on labor, its influence on the ensuing course of labor must be examined. A uterotonic agent should shorten subsequent phases up to a certain limit defined by an "ideal" dilatation curve. If the material is given at or before the onset, as in induction, the whole course of labor should reflect its influence. When given during the latent phase, the succeeding active phase and second stage should be affected; when given after the active phase is well underway, only the ensuing second stage will be shortened. If administered just prior to delivery, the preceding phases cannot possibly be influenced; here it can only act as an aid to delivery with little or no influence upon the second stage. It is because of these presuppositions that the categories of "elective" patients were designed. These include parturients who received the drug for induction or stimulation of normal labor in progress, but not for the purpose of treament or as an aid to delivery. Elimination of 176 patients who received the drug during the second stage and 392 who required therapy for various dysfunctional states leaves 640 "elective" (electively treated) patients suitable for the evaluation of drug action. Indeed it is only this group of patients in which the effect of the drug can be determined.

The "ideal" dilatation curve with reference to nulliparous labor represents a composite of true undisturbed parturition. The data for this control group were taken from a series of 200 patients at term with adequate pelves, vertex presentations, occipitoanterior position, and normal progression of labor resulting in an uncomplicated vaginal delivery of a normal-sized infant.[3] Their dilatation curves describe an unimpeded parturitional process and serve to evaluate modalities that are potentially beneficial to the labor process.

The cervical dilatation curve for each individual patient was divided into phases for a numerical expression of the individual components and their relation to the precedent administration of the drug. Comparison of the composite data of these curves were then made with mean values, obtained in similar fashion, from a control clinic population, and standard tests of significance applied ($p < 0.01$).

The basic difference in the progress of nulliparous and multiparous labors necessitates separate analyses of these groups. The significant data for these groups are reproduced in Table II. Figs. 1 and 2 were constructed to elucidate the difference between treated and untreated control groups. The electively stimulated nulliparous group, when compared with the mean nulliparous control, demonstrated significant reductions in the active phase brought about by a shortening of the deceleration phase and a more rapid rate of dilatation. Although the latent phase was shortened, the difference was not statistically significant. The time elapsed from onset to delivery was shortened by 2.69 hours. These specific changes produced in the treated group of patients were clearly in the direction of the previously defined "ideal" labor curve (Fig. 1).

When contrasted with this "ideal" nulliparous control, a comparable group of nulliparous (sparteine) inductions yielded data that indicated a significant shortening of the latent phase from 7.1 to 4.8 hours, but no further effect upon the length of the active phase and second stage. One can infer that the drug had shortened the ideal pattern without producing precipitate labors. Its uterotonic effect is evident.

A similar pattern emerges from an analysis of multiparas stimulated with sparteine

Table II. Statistical analysis of the cervical dilatation–time curves and their components

	No. of patients	*Latent phase (hours)*	*Active phase (hours)*	*Maximum slope (cm./hr.)*	*Deceleration (hours)*	*Second stage (hours)*
Mean primiparas (control)	500	8.6 ± 0.27	4.9 ± 0.15	3.0 ± 0.08	0.9 ± 0.05	1.0 ± 0.04
Elective primiparas	134	7.4 ± 0.37	3.5 ± 0.25*	4.2 ± 0.30*	0.7 ± 0.09*	0.9 ± 0.07
Ideal primiparas (control)	200	7.1 ± 0.28	3.4 ± 0.11	3.5 ± 0.13	0.7 ± 0.05	0.8 ± 0.04
Primiparous inductions	31	4.8 ± 0.70*	3.3 ± 0.48	4.0 ± 0.57	0.8 ± 0.13	0.7 ± 0.08*
Mean multiparas (control)	500	5.3 ± 0.19	2.2 ± 0.07	5.7 ± 0.16	0.2 ± 0.01	0.3 ± 0.01
Elective multiparas	506	5.4 ± 0.17	1.9 ± 0.05*	7.2 ± 0.20*	0.1 ± 0.02*	0.1 ± 0.01*
Multiparous inductions	152	3.3 ± 0.25*	1.7 ± 0.08*	7.3 ± 0.36*	0.1 ± 0.01*	0.2 ± 0.02*

*Designates statistical significance ($p < 0.01$).

(Fig. 2). The elective group showed a significant shortening of the active phase (increased rate of dilatation and shorter deceleration phase) and second stage, while in multiparous inductions every interval from onset to delivery was significantly reduced. The over-all reduction in the total duration of labor was found to be 0.4 hour for the elective group and 2.7 hours for the inductions.

Fetal and maternal complications. Among the 1,208 treated patients whose dilatation curves were suitable for analysis, the complications listed in Table III were recorded. Nine patients had relative cephalopelvic disproportion which led to midpelvic arrest in 7. Four of these required cesarean section, 1 a midforceps delivery, 1 required low forceps, and 1 ended in a spontaneous delivery.

There were 8 stillbirths and 3 neonatal deaths. The stillbirths included 2 premature babies (1,400 and 1,770 grams, respectively), 1 anencephalic monster, 1 macerated baby with erythroblastosis fetalis, 1 traumatic death due to breech delivery with double nuchal hitch, and 3 in which no reason was forthcoming. The 3 neonatal deaths were attributed to prematurity (1,100 grams), agenesis of the right lung with coarctation of the aorta, and severe erythroblastosis fetalis.

Of interest to the current study was the fact that a "tense uterus" was recorded in the charts of 3 patients who received the drug during labor. None of them had a true tetanic contraction and all 3 had normal spontaneous deliveries resulting in healthy, live infants.

The administration of the drug to the parturient does not seem to have any deleterious effect upon the baby as shown by an analysis of the Apgar scores. In Table IV a

Table III. Maternal complications in 1,208 patients

Complication	*No.*	*Remarks*
Diagnosed primary inertia	4	
Diagnosed secondary inertia	2	
Pre-eclampsia	18	1 with pre-existing hypertensive disease
Rheumatic heart disease, inactive	3	
Midpelvic arrest	2	Trial of labor
Fibromyomas of the uterus	1	
Placenta previa, marginal	2	Cesarean section
Prolapsed cord	1	Cesarean section
Retained secundines	2	
Abruptio placentae	2	Cesarean section
Impacted shoulders	5	
Cervical stenosis	1	
Iron deficiency anemia	12	
Pneumonitis	1	
Essential hypertension	1	
Schizophrenia	1	
Spontaneous pneumothorax	1	During antepartum course
Postpartum atony with hemorrhage	5	Retained secundines
Postpartum hemorrhage	2	
Postpartum hypertension	5	Postpartum oxytocic unknown

control group of 15,348 untreated clinic patients[4] are compared with 804 sparteine treated patients whose scores were available. The incidence of fetal distress during labor as evidenced by fetal bradycardia (17 in 1,208) was actually well below the over-all incidence in the clinic population.[5]

Failures. Of the 1,364 patients who received sparteine sulfate for the purpose of induction or stimulation of labor, there were 156 in whom the criterion of success was not fulfilled (Table I). Excluding 7 patients with inadequate records and 89 who received oxytocin in addition to sparteine there remained 60 patients who represented true failures. The causes of these failures were thoroughly investigated. In 42 the cervix was considered to be unripe to varying degrees; these patients were unprepared for labor and, therefore, unfit for induction, as shown by the fact that none was delivered in less than 24 hours, 23 within 7 days, and 19 more than 1 week later. Seven of the 60 failures were associated with severe cephalopelvic disproportion and labor was terminated by cesarean section. An additional 7 were subjected to cesarean section because of fetal distress. For the remaining 4, no adequate reason for the failure could be found. If all the instances where oxytocin was used in conjunction with sparteine sulfate are counted as failures, the drug may have failed in a maximum of 142 or 10.4 per cent (by deleting the 14 incidental abdominal deliveries) and a minimum of 93 or 6.8 per cent (by deleting 7 inadequate records and 42 patients with unripe cervices).

Postpartum period

That the human postpartum uterus contracts under the influence of sparteine sulfate has been objectively documented by Kraus.[6] Although his intrauterine pressure measurements clearly showed this effect, his results are somewhat obscured by his use of admixtures of pentamethylenetetrazol given to enhance the uterotonic effect. Numerous other clinical investigators have also used sparteine sulfate in the postpartum period[1] but their reports are based on clinical impressions rather than on tangible measurements, and such reports cannot be used to evaluate the specific postpartum effect of sparteine.

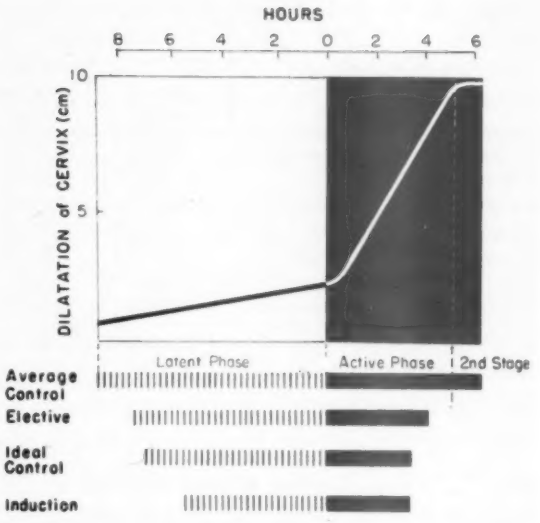


Fig. 1. Graphic comparison of the phase components for nulliparous controls and treated patients. The upper portion depicts the average cervical dilatation–time curve for 500 nulliparous controls. In the lower portion, the four groups are contrasted according to the length of the latent phase (striped) and the sum of the active phase and second stage (solid blocks), showing the relative reductions in durations resulting from stimulation with sparteine sulfate.

The pharmacologic characteristics of an oxytocic drug for the postpartum period are quite different from those expected for its intrapartum use. Here, the drug should produce prolonged tetanic uterine contractions and reduce the blood loss and initiate involution, accomplishing these ends without undesirable side effects. The manner in which this portion of the study was carried out was similar to previously reported evaluations of ergot derivative and oxytocin preparations.[7, 8] Because of the well-defined clinical criteria and the relative paucity of complicating variables, a smaller population sample was required. The effect of sparteine sulfate on the incidence of atony, the variations in blood loss, and its side effects were examined. The data are summarized in Table V.

Patients and procedure. A series of 200 consecutive patients were given 300 mg. of

sparteine sulfate intramuscularly at the termination of the third stage. The findings were then compared with those in a control group of 200 patients who received no prophylactic uterotonic agent. All cases were evaluated with reference to blood pressure levels before and during pregnancy and labor, their relative durations of labor, durations of the third stage, sedative-analgesic effects and anesthesia during labor and delivery, delivery trauma, estimations of blood loss at delivery, and antepartum and postpartum hemoglobin levels. Pertinent postpartum observations included notations of occurrence and degree of nausea and emesis, blood pressure and pulse rate observations at 5 minute intervals for 1 hour after delivery, and the responsiveness of the uterus to medication with particular attention to atony.

Treated and control groups were comparable by age, parity, gestational age, labor aberrations, length of third stage, sedation, and anesthesia, with the single exception of a slightly higher incidence of conduction anesthesia in sparteine-treated patients. Though this was statistically not significant, it might represent a bias in view of the known depression of uterine tone with general inhalation anesthetics.

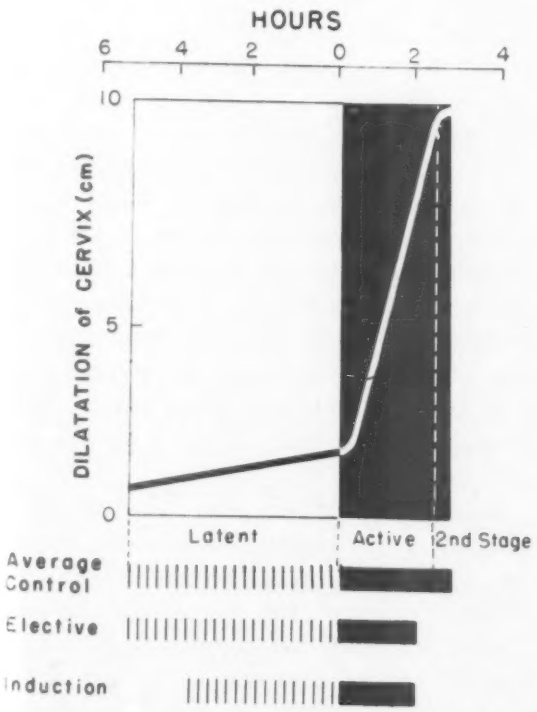


Fig. 2. Graphic comparison of the phase components for multiparous treated and untreated patients. The upper portion of the graph depicts the average dilatation curve for 500 multiparous controls. In the lower portion, the three groups are contrasted according to the length of the latent phase (striped) and the sum of the active phase and second stage (solid blocks).

Uterine atony. Qualitative assessments of uterine atony in the immediate postpartum period were made on all patients. Excluding slight or doubtful atony (requiring no treatment other than uterine massage), an incidence of 4.5 per cent of atony was encountered in the sparteine-treated group as compared with a control incidence of 20.9 per cent. The difference between these values is statistically significant.

In its uterotonic effect, sparteine stands up reasonably well when compared with other oxytocic agents. Sparteine is, however, inefficient in maintaining uterine tonicity over a longer period. The incidence of late atony (that is, atony occurring more than 1 hour after delivery) was 5.7 per cent for the control group and 6.5 per cent for the sparteine-treated group while under comparable circumstances, oxytocin maintained its action satisfactorily.[7, 8]

Blood loss. Estimates of blood loss for the immediate postpartum period are notoriously incorrect. The loss of blood following delivery of the placenta is partly but not wholly dependent on atony, for injuries of the cervix, vagina, and episiotomy may contribute to this loss. For this reason, estimates of blood loss should be interpreted with caution.

Accurate measurements of blood loss would be difficult to carry out on the large numbers of patients needed for the present statistical interpretation. In order to simplify such an analysis, a standardized procedure of gross estimation in current use at this institution was used. This divides the patients into three easily distinguishable groups, namely, minimal blood loss (under 250 ml.), moderate (250 to 500 ml.), and

Table IV. Distribution of Apgar scores

Score	*General clinic population (%)*	*Sparteine successes (%)*	*Sparteine failures (%)*
10	14.5	13.3	22.1
9	29.2	38.0	33.7
8	24.3	21.6	9.1
7	10.8	12.5	9.1
6	6.0	3.9	5.2
5	4.1	3.6	2.6
4	3.1	2.6	7.8
3	2.6	2.6	3.9
2	2.6	0.7	1.3
1	2.4	1.4	2.6
Total No. of babies	15,348	727	77

Table V. Incidence of postpartum atony, blood loss, and side effects

	Sparteine (%)	*Controls (%)*	*Remarks*
Atony			
Immediate	4.5	20.9	Significant
Late (more than 1 hour)	6.5	5.5	Not significant
Blood loss			
Moderate	27.5	39.5	Not significant
Severe	3.0	2.0	Not significant
Hypertension			
Antepartum	12.0	10.5	Not significant
Intrapartum	14.5	24.5	Not significant
Postpartum	20.5	33.5	Not significant
Emesis	1.5	4.5	Not significant

marked (over 500 ml.). For the analysis, only the moderate and marked blood loss groups are considered. The latter group usually required one or more whole blood transfusions, thus presenting documentary evidence of excessive blood loss. The data of Table V indicate no significant difference between treated and control groups.

Side actions. The signs and symptoms of greatest interest to the clinician are cardiovascular and gastrointestinal manifestations. Variations in blood pressure, nausea, and vomiting could be attributed to the administration of the drug. The blood pressure can be measured with considerable accuracy and the incidence of vomiting can be reliably recorded, but nausea was felt to be too subjective a symptom for the purpose of evaluation.

In order to detect the variations in blood pressure which might occur after the administration of the drug, recordings were made at 5 minute intervals for 1 hour following delivery. A transitory rise in blood pressure may occur in otherwise normal postpartum patients as well as in those with unrecognized toxemia; hence, the mere occurrence of this event is not necessarily attributable to the drug. It is necessary to include an examination of the incidence of antepartum, intrapartum, and postpartum hypertension in both groups.

Blood pressure elevations were divided into three groups as previously defined; an increase of 15 mm. Hg systolic and/or 10 mm. Hg diastolic above an initial level of 140/90 is considered a "mild" elevation; an increment of 25/20 mm. Hg was considered "moderate"; and above that was considered "severe." Since the incidence of the last group in treated and untreated patients was too low for statistical comparison, the data for moderate and severe responses were combined for the presentation in Table V. As can be seen from the data in Table V, the routine use of sparteine sulfate in the postpartum period does not produce a detectable increase in the incidence of postpartum hypertension. Ergonovine and methylergonovine but not oxytocin are known to be responsible for transitory elevations in blood pressure beyond that expected from statistical survey.

Although potentially less dangerous than transient hypertension, nausea, and vomiting are highly undesirable side effects. The incidence figures for documented emesis (Table V) show no significant difference between treated and control groups. Sparteine, like oxytocin, is devoid of emetic effects and differs from the previously tested ergot derivatives.[7]

Comment

From the pharmacologic point of view, the most convincing evidence for the stimu-

lating action on the human uterus is its reduction in the incidence of uterine atony during the postpartum period. This same stimulating action was also demonstrated to a lesser degree under various conditions of normal and abnormal labors. Dysfunctional states could not be evaluated to a degree sufficient to warrant detailed reporting at this time because of the difficulty in classifying these cases for study, the lack of comparable control groups, and their paucity of numbers.

The present statistical study does not give any information on the mechanism of action but allows only a prediction of its effects on a variety of obstetric problems. When administered during the intrapartum period, it leads to reduction of the length of labor, presumably accomplished by a more efficient activity of the myometrium. Following its administration, all phases of the first stage and the second stage are shortened without necessarily producing an excessively rapid rate of cervical dilatation even if given in larger or more frequent doses than those recommended.

For the induction of labor, the cervix must be "ripe," labor must be "inducible" according to the commonly accepted criteria, and the patient must be appropriately screened. If these conditions are not met, labor cannot be enforced and attempts at induction with sparteine before term will probably fail. If labor can be initiated, its pattern will approach an ideal one and its length reduced. This can be brought about without intravenous infusions and their attendant cost and dangers.

For the stimulation of labor in progress, the drug is best administered during the early part of the first stage if the objective is a speedy (shortened) yet normal labor. It should be administered in 150 mg. doses which can be repeated at hourly intervals. Successful delivery without the aid of other agents can be anticipated in 90 per cent of patients after only 3 doses. Should the drug fail to produce an adequate response after 3 successive injections, no harm has been done and other, more forceful agents can then be used if necessary. It is this characteristic which contributed to the popularity and the extensive use of sparteine sulfate in this institution.

Summary

The clinical application of sparteine sulfate was retrospectively evaluated on 1,364 intrapartum and 200 postpartum patients. For the intrapartum evaluation, an average of 1.9 doses of 150 mg. at hourly intervals with a minimum of 1 and a maximum of 11 doses were given. The effects on the cervical dilatation–time curve were studied and compared with those of average multiparas and nulliparas. A statistically significant shortening of labor results after the administration of sparteine. If sparteine is given during the first stage (latent and active phase of dilatation curve), the total length of nulliparous labors is reduced by 2.7 hours, and that of multiparas by 0.4 hour. If it is given before the onset of labor, for the purpose of induction, all phases of the subsequent cervical dilatation curves are shortened, producing an ideal labor pattern with an abbreviated latent phase. When compared to that in the appropriate control groups, the length of labor for inductions in nulliparas was shortened by 5.6 hours, that of multiparas by 2.7 hours.

The incidence of fetal and maternal complications for this group did not differ from that of the general hospital population. There was no increase in fetal distress and no adverse effect upon the baby as shown by an analysis of the Apgar scores.

When sparteine sulfate was used as a prophylactic postpartum oxytocic, its uterotonic characteristics could be demonstrated by a reduction in the incidence of uterine atony. This effect is brief and for this reason the drug offers no advantage over oxytocin. For the induction or stimulation of labor, on the other hand, the drug is unique. Its demonstrated lack of side effects, relative safety, and ease of administration justified and brought about its extensive use in this institution.

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Spontaneous premature rupture of the fetal membranes

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ONE of the less common but more fundamental aspects of the prematurity problem concerns spontaneous premature rupture of membranes. Because of differences in definition, its incidence varies widely and, since the etiology remains obscure, prevention of this accident is difficult and control is controversial. To help clarify this and other facets of prematurity, this study was designed for three purposes: (1) to review 6 years of clinical experience with spontaneous premature rupture of the membranes, (2) to assess the role of infection in this complication as a cause of perinatal morbidity and mortality, and (3) to investigate the etiology of spontaneous premature rupture of membranes by a study of uterine contractility patterns during pregnancy.

Materials and methods

In the Department of Obstetrics and Gynecology at the University of Colorado Medical Center, from July 1, 1952, to June 30, 1958, there were 7,329 deliveries, 468 of which were associated with spontaneous premature rupture of membranes.

The definition of premature rupture of membranes in this study was arbitrarily set at 12 or more hours before the onset of labor. This criterion was established because perinatal morbidity and mortality remained minimal until 12 to 24 hours had passed. There were 21 mothers whose membranes were ruptured artificially who had a latent period of more than 12 hours. These patients were excluded from the current study. During this same 6 year period, there were 81 patients with spontaneous premature rupture of the membranes who were hospitalized on the Control of Prematurity Program sponsored by the Children's Bureau. This special hospitalized group was compared to 269 other patients with spontaneous premature rupture of the membranes who were allowed bed rest at home. The latter study was done to gauge the importance of early and prolonged hospitalization versus treatment at home for patients with spontaneous premature rupture of the membranes. Another 5 patients within the total group of 468 were studied at 2 week intervals from the twentieth week of pregnancy to delivery with respect to their uterine contractility patterns.

Results

Incidence. In this clinical study of 7,329 deliveries, 468 patients had spontaneous pre-

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This study was carried out with the aid of grants from the Division of General Medical Sciences, United States Public Health Service, Playtex Park Research Institute, and the Children's Bureau in cooperation with the Colorado State Department of Public Health and the University of Colorado Medical Center.

mature rupture of membranes, an incidence of 6.3 per cent. Of the 468 patients who had spontaneous premature rupture of the membranes, 157 or 32.6 per cent were delivered of premature infants. The hospital premature birth rate approximates 13 per cent.

Complications during pregnancy and labor. In an analysis of 468 patients with spontaneous premature rupture of membranes, there were 346 or 74 per cent with no previous medical or obstetrical complications. In the remaining 26 per cent, urinary tract infection was the most common complication.

In the present pregnancy there were no complications in 384 (82 per cent). Again, the remaining complications included toxemia and urinary tract infections (Table I).

Study of labor complications revealed 12 instances of antepartum hemorrhage and 8 patients with prolapse of the umbilical cord.

Table I. Complications of pregnancy (spontaneous premature rupture of membranes)

	Pregnancy	
	Previous	*Present*
None	346	384
Urinary infections	64	28
Prolonged labor	31	0
Toxemia	19	41
Hydramnios	0	8
Leiomyomas	0	4
Other	8	3
Total	468	468

Table II. Morbidity due to infection in mothers whose infants survived (spontaneous premature rupture of membranes)

Weight groups (grams)	*Mothers with SPRM*	*Infants with infection*	*Per cent infants with infection*
401 to 1,000*	1	1	100.0
1,001 to 1,500	11	5	45.5
1,501 to 2,000	34	4	11.8
2,001 to 2,500	85	2	2.4
2,501 or more	296	6	2.0
Total	423	18	4.3

*Infants weighing 401 to 1,000 grams classified as immature.

The 6 year incidence of prolapsed cord in this hospital was 0.5 per cent, while in this study series of 468 patients with premature rupture of membranes, the incidence increased to 1.7 per cent. The occurrence of prolapsed cord parallels the increased frequency of breech presentation in this study group and was 7.3 per cent or over twice the usual figure.

Neonatal morbidity associated with spontaneous premature rupture of membranes. In the total group of 423 infants who survived, 18 or 4.3 per cent presented some type of infection during the neonatal period (Table II). Among these were 6 babies with diarrhea, 3 with septicemia, 2 with omphalitis, 2 with conjunctivitis, 2 with moniliasis, 1 with rhinitis, 1 with bacteremia, and 1 with pneumonia.

Only 3 of the 6 infants with diarrhea had positive cultures for pathogens and 1 of these occurred during an epidemic of diarrhea in the nursery. The pneumonia was attributable to aspiration of meconium at the time of delivery. The cases of conjunctivitis developed long after delivery and were unassociated with spontaneous premature rupture of membranes in the mother. Two cases of omphalitis, 2 of septicemia, 2 of diarrhea, and 1 of moniliasis were most likely caused by premature rupture of the membranes. Thus, a detailed study of each of these infants suggested that the majority of the neonatal infections were not the immediate result of spontaneous premature rupture of the membranes in the mother. If the 11 doubtful cases of neonatal infection are excluded, the corrected neonatal morbidity is 1.7 per cent. Neonatal morbidity increased from 1.3 per cent when membranes were ruptured less than 24 hours to 13.3 per cent when membranes had been ruptured for 3 weeks or more. Likewise, the longer membranes are ruptured, the greater is the risk of perinatal death (Table III and Fig. 1).

Perinatal mortality associated with spontaneous premature rupture of membranes. The total perinatal mortality for all deliveries for the 6 year period was 4.0 per cent as compared to 10.9 per cent in infants

Table III. Perinatal morbidity and mortality (spontaneous premature rupture of membranes)

Duration of ruptured membranes	*Mothers with ruptured membranes*	*Infants with infection*		*Infant deaths*	
		No.	*%*	*No.*	*%*
12 to 23 hours	154	2	1.3	4	2.6
24 to 48 hours	124	4	3.2	12	9.7
49 to 72 hours	57	3	5.3	4	7.0
73 to 120 hours	55	4	7.3	11	20.0
121 hours to 7 days	37	1	2.7	7	18.9
8 days to 14 days	26	2	7.7	7	26.9
15 days or more	15	2	13.3	7	46.7
Total	468	18	3.8	52	11.1

whose mothers had spontaneous premature rupture of the membranes (Tables IV and V).

When perinatal mortality is compared by weight gram groups, the perinatal loss in the study cases was found to be very similar to the over-all 6 year group except for infants weighing 2,500 grams and over. Perinatal mortality in the study series, which is about triple that of the 6 year group, is mainly accounted for by the infant losses in the term group. In weight groups below 2,500 grams in either series, the greatest single hazard to the infant is prematurity and the complications associated with it. The major cause of neonatal mortality in infants whose mothers had premature rupture of membranes was abnormal pulmonary ventilation. Anoxia accounted for the largest number of fetal deaths (Table VI).

Eight of the stillborn infants weighed over 2,500 grams and made up half of the number of stillborn infants. Clinical conditions associated with the pathologic diagnoses of anoxia and maceration in the stillborn infants were prolapsed cord, breech extraction, and toxemia. Infection did not contribute significantly to the number of stillborn infants.

Hospitalization versus treatment at home. During the 6 year study, from 1952 to 1958, the Children's Bureau sponsored a continuing program within the Department of Obstetrics and Gynecology, namely the Control of Prematurity Program. Nine infants from this group of mothers died in the perinatal period. A control group of 269 patients were allowed to go home after 72 hours of observation. There were 28 perinatal deaths in this group. The total mortality was approximately 10 per cent in each group and causes of death were essentially the same in each group (Table VII).

Uterine contractility patterns during pregnancy in patients who had spontaneous premature rupture of membranes. Five patients were studied from the twentieth week of pregnancy until delivery. These 5 volunteers

Table IV. Perinatal mortality (all deliveries)

Weight groups (grams)	*Total births*	*Total deaths*	*Perinatal mortality (%)*
401 to 1,000	64	58	90.6
1,001 to 1,500	84	56	66.7
1,501 to 2,000	158	39	24.7
2,001 to 2,500	625	43	6.9
2,501 or more	6,003	79	1.3
Total	6,934	274	4.0

Table V. Perinatal mortality (spontaneous premature rupture membranes)

Weight groups (grams)	*Total births*	*Total deaths*	*Perinatal mortality (%)*
401 to 1,000	20	19	95.0
1,001 to 1,500	22	9	40.9
1,501 to 2,000	38	8	21.0
2,001 to 2,500	97	5	5.2
2,501 or more	300	11	3.7
Total	477*	52	10.9

*This 477 equal 468 plus 9 infants from 9 sets of twins.

were part of a larger study group whose uterine contractility and urinary steroid metabolites were carefully measured at 2 week intervals during the latter half of pregnancy.[1] From these 5 patients, observations were made that uterine contractility was frequently excessive long before spontaneous premature rupture of the membranes occurred (Table VIII and Fig. 2). From previous studies it was observed that when patients developed pyelonephritis, cystitis, cervicitis, or vaginitis there was concomitant hypermotility of the uterus. Study of myometrial contraction patterns in patients with hypermotility revealed the origin of contractions to be in the middle or lower portions of the uterus. In general, this type of contraction pattern tended to keep the cervix from dilating. However, when activity in the upper portion of the uterus exceeded that in the lower segment, the cervix tended to efface and dilate with or without spontaneous premature rupture of membranes.

Comment

There has been widespread opinion that infection plays a major role in production of perinatal mortality in spontaneous premature rupture of membranes. Cron and Brown[2] state that before the advent of chemotherapeutic agents, intrapartum infection was a dire threat to the outcome of pregnancy. Flowers and his group,[3] in their studies on 1,185 patients with premature rupture of membranes, reported 75 fetal and neonatal deaths. Of these deaths, 23 or 30.7 per cent were due to amnionitis and intrapartum infection. The Colorado series did not show infection to play so great a role. However, part of this discrepancy may be due to inclusion of atelectasis and hyaline membrane disease under the infection classification in the North Carolina study. Analysis of infection deaths in the Colorado series showed 1 case of intrapartum pneumonia in a stillborn infant and 3 neonatal deaths due to pneumonia. Two of the neonatal pneumonias were not the result of ruptured membranes. Both of these infants had been discharged from the hospital and several weeks later one developed pneumonia from aspira-

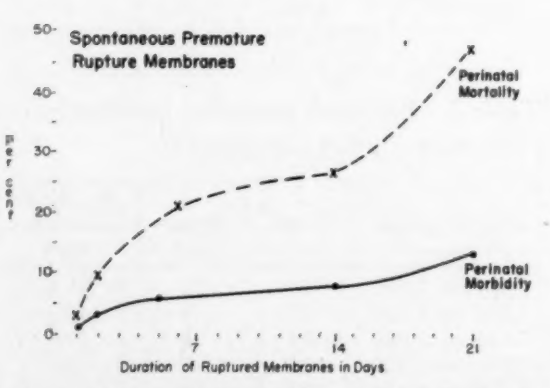


Fig. 1. This graph shows that perinatal mortality and morbidity increase gradually if membranes are ruptured over 24 hours.

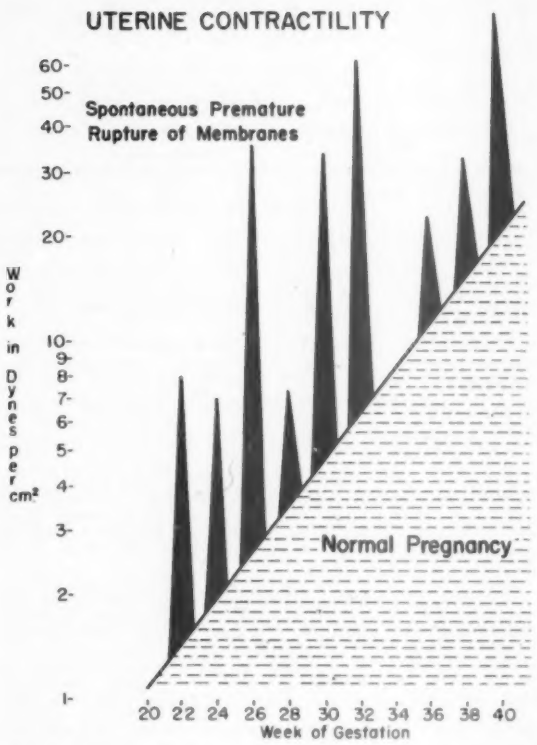


Fig. 2. The spikes superimposed upon this normal pattern of uterine contractility are individual values from 5 patients whose pregnancies ended in spontaneous premature rupture of membranes. The solid diagonal line is the ninty-fifth percentile which was established from 40 normal patients on whom 328 uterine motility records were obtained during the last 20 weeks of normal pregnancy. The cross-hatched area shows, in semidiagrammatic form, that 95 per cent of normal patients exhibited increasing uterine activity as pregnancy progressed to term.

tion of milk and the other had congestive failure due to congenital heart disease. Only 2 perinatal deaths were directly attributable to infection.

It has been shown that penicillin, streptomycin, chloramphenicol, and tetracycline cross the placenta. In the case of penicillin, Fonsman[4] reports that the concentration of penicillin in the cord blood reaches about half that in the mother's blood. Chloramphenicol and streptomycin traverse the placenta readily, but their use has been discontinued, particularly in the case of chloramphenicol because of its toxic effect on the fetus.[5] Penman and Wilson[6] agree that oxytetracycline and tetracycline cross the placenta, but state that, in the case of oxytetracycline, a priming dose of 750 mg. orally is required to obtain therapeutically effective levels in the fetus. Guilbeau and Eastman[7] have presented data which indicate that administration of penicillin during the latent period has no effect on perinatal mortality. It also appears, according to Flowers and his group,[3] that the wide-spectrum antibiotics would be ineffective during the whole latent period and may even be contraindicated since the balance of the vaginal flora might be affected. A majority of clinicians believe that the use of wide-spectrum antibiotics is indicated only after the onset of maternal infection during labor and in the puerperium.

The clinical impression gained from this study in which some patients with spontaneous premature rupture of membranes were hospitalized and treated, while others were sent home, supports the belief that antimicrobial therapy during the latent period is unnecessary. Analysis of the 52 perinatal deaths revealed that 14 of the mothers had received antibiotics prophylactically. Two of these 14 perinatal deaths were caused by infection. Fifteen mothers received antibiotics therapeutically and one of these 17 perinatal deaths was due to infection. Nineteen mothers did not receive any type of antimicrobial agents and one of these 21 deaths was due to infection. This further supports the impression that antibiotics given to mothers with spontaneous premature rupture of membranes do not alter perinatal mortality.

In Sangalang's study,[8] where positive cultures were obtained from the endocervix or the amniotic fluid (16 out of 60, or 25 per cent), the more common organisms found were *E. coli* (43.7 per cent), hemolytic streptococci (37.5 per cent), and staphylococci (12.5 per cent). All of these organisms were sensitive to penicillin or oxytetracycline. In his series of 60 patients with premature rupture of membranes, he

Table VI. Causes of perinatal deaths (spontaneous premature rupture of membranes)

Neonatal	
Atelectasis	10
Hyaline membrane	6
Hemorrhage	5
Malformations	3
Pneumonia	3
No diagnosis	4
No autopsy	4
Total	35*
Stillborn	
Anoxia	7
Maceration	4
Hemorrhage	4
Malformations	1
Pneumonia	1
No diagnosis	0
No autopsy	0
Total	17†

*Three infants weighed over 2,500 grams.
†Eight infants weighed over 2,500 grams.

Table VII. Selected patients with spontaneous premature rupture of membranes*

	No. of mothers	*Perinatal deaths*	
		No.	*%*
Patients hospitalized 72 hours to 14 days	81	9	11.0
Patients observed 72 hours and sent home	269	28	10.0

*Part of a study on the Control of Prematurity Program sponsored by the Children's Bureau in cooperation with the Colorado State Department of Public Health and the University of Colorado Medical Center.

Table VIII. Clinical data in 5 patients whose pregnancies terminated in spontaneous premature rupture of membranes

Patient	*Age*	*Parity*	*Week of ruptured membranes*	*Week of delivery*	*Weight of infant in grams*
H. G.	27	5	32	33	2,030
L. T.	24	0	34	35	2,300
V. W.	25	2	39	40	2,510
B. T.	24	1	39	40	3,410
D. W.	27	2	38	38	2,640

Table IX. Experimental data in 5 patients whose pregnancies terminated in spontaneous premature rupture of membranes

	Uterine work in dynes/cm.² (weeks of pregnancies)*										
Patient	*20*	*22*	*24*	*26*	*28*	*30*	*32*	*34*	*36*	*38*	*40*
H. G.	0	0	7	34.4	7	33.1	80.5				
L. T.	0	8	0	11.5	0	0	22.5				
V. W.	0	0		10.6	0	12.5	12.3		21.9	32.2	134
B. T.			0	2.1	0		0	0	0	1.4	
D. W.		0	2	0	0	1.0	0	1.0	2.4	26.0	

*Formula used to calculate work in any segment of the uterus: $W = (\frac{1}{3}\ IT + [D-T]\ I) \times S$. (Reynolds et al.: Arch. Int. Pharmacodyn. 78: 203, 1949.)

treated them with penicillin and triple sulfonamide cream or oxytetracycline during the whole of the latent period and during labor. He attributed his low maternal morbidity and minimal perinatal mortality to the use of prophylactic antibiotics.

For many years there has been the opinion that inherent weakness of the membranes was the cause of premature rupture of membranes. Duncan,[9] in 1868, stated that the strength of the membranes depends mainly on the amnion. His studies, which received support by Danforth in 1953,[10] show that thickness of the membranes have very little to do with their bursting tensions. In an effort to prove or disprove previously mentioned theories on intrinsic variation in the membranes, Danforth conducted a series of experiments on bursting tensions of membranes that had been involved in spontaneous premature rupture of membranes. He found that the average tensions on the membranes necessary to burst them were in the range of 23 cm. Hg per centimeter to 26 cm. Hg per centimeter. Caldeyro and associates[11] have found intrauterine pressure in normal labor to be about 35 mm. Hg. Occasionally pressures as high as 50 mm. Hg have been recorded. Thus, when intrauterine pressure is 33 mm. Hg, the tension on the membranes is 8.75 cm. Hg per centimeter and when intrauterine pressure is 50 mm. Hg, tension on the membranes is 12.5 cm. Hg per centimeter. Consequently, Danforth felt that there was an adequate safety factor in the membranes and that intrauterine pressures alone would be insufficient to rupture the membranes. However, sections of membranes taken for his study were selected at random and were not confined to the area at or near the cervical os where local factors may exert a weakening effect.

Many investigators during the past century have described inflammatory processes in the membranes examined histologically from women who had spontaneous premature of membranes. However, the incidence of this finding in any large series of cases is usually small and is more commonly associated with late abortions. From the literature it is not clear to what extent developmental defects of inflammatory

processes contribute to the etiology of premature rupture of membranes. As a result of the present study, it seems reasonable to suggest that one mechanism of the etiology of spontaneous premature rupture of membranes is maternal infection; particularly, latent infection in the urogenital tract which causes or is associated with increased uterine contractility.

Kjessler,[12] from conclusions on his own series of cases with spontaneous premature rupture of membranes, reports that physical and psychic trauma play a minimal role in production of premature rupture of membranes. In the present study of 468 patients who had spontaneous premature rupture of membranes, trauma was not listed as an etiological agent in a single case.

Current measures employed at Colorado General Hospital to control the problem of spontaneous premature rupture of membranes consists mainly in vigorous treatment of any overt or suspected maternal infection, particularly infection of the urogenital tract. Reduction of excessive uterine contractility has been attempted principally by bed rest at home or in the hospital. Management of patients whose membranes have already ruptured consists of bed rest in the hospital or bed rest at home if labor does not ensue within 72 hours. The spontaneous onset of labor is awaited if pregnancy is less then 37 weeks; labor is induced if the patient is at 37 weeks or more of gestation. Antimicrobial therapy is reserved for those mothers who have infection or who go into active labor.

Summary and conclusions

1. In a clinical study of 7,329 deliveries, 468 patients had spontaneous premature rupture of the membranes, an incidence of 6.3 per cent.

2. In approximately 75 per cent of patients with spontaneous premature rupture of membranes, there was no clear-cut history of medical or obstetrical complications. In the remaining 25 per cent, toxemia and urinary tract infections were the chief complications.

3. Neonatal morbidity due to infection was 4.3 per cent. When this figure was corrected for infection associated primarily with premature rupture of the membranes, the mortality rate was only 1.7 per cent.

4. Both neonatal morbidity and mortality due to infection increased progressively when the latent period between premature rupture of membranes and delivery exceeded 24 hours.

5. Total perinatal mortality during the 6 year period was 4.0 per cent. In patients with spontaneous premature rupture of membranes, the mortality increased to 10.9 per cent. This increase was due primarily to the perinatal loss of term-sized stillborn infants.

6. In this series, infection did not play a great role in perinatal mortality in mothers who had premature rupture of membranes. Four infants or 7.7 per cent died because of infection. If this is corrected for infection deaths directly attributable to spontaneous premature rupture of membranes, the number is 2 or 3.5 per cent.

7. The main causes of neonatal mortality in patients whose membranes rupture prematurely were atelectasis, hyaline membrane disease, and pulmonary hemorrhage.

8. The major cause of fetal death was anoxia due to prolapsed cord, breech delivery, and toxemia.

9. Uterine hypermotility preceded by many weeks or months spontaneous premature rupture of membranes. This increased uterine contractility may be an additional factor predisposing to early rupture of normal or abnormal fetal membranes.

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Delayed and prolonged labor, placental retention, and hemorrhages in rabbits

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PARTURITION in women is a unique process in that the delivering muscle bag, the uterus, selectively expels the fetus while at the same time this "hostile" contractile environment permits the placenta to remain attached and functional for a longer period. In addition to this everyday demonstration of asymmetrical function, the human uterus occasionally displays functional asymmetry in an exaggerated form by delivering one fetus of a pair of twins, while retaining the other fetus for several weeks in spite of the open birth canal.[7, 8, 17]

It is a textbook statement[13] that selective delivery of the fetus and the placenta in women is attained by the "splint-like" action of the fetus on the contractile uterus. Such a mechanism may indeed promote placental attachment. But the importance of a solely *mechanical* splint is largely ruled out by the elegant experiments of van Wagenen and Newton.[24] They demonstrated that, after removal of the fetus at midpregnancy in the rhesus monkey, the placenta remains in utero until term, when it is delivered. Furthermore, it is known from clinical experience that the human placenta may also remain in utero for several days after the birth of the fetus in cases with no evidence of abnormal placental attachment.[13]

It is now well established that in women progesterone production shifts in early pregnancy from the corpus luteum to the placenta.[21] It has also been demonstrated that progesterone is capable of blocking the propagated activity of the rabbit myometrium, an effect which drastically modifies uterine contractility.[1, 6-9, 18, 22, 23]

In order to account for the selective delivery in women of the fetus and the placenta or of a pair of twins, a theory has been proposed.[7-10] It was suggested that the human uterus is functionally asymmetrical and that this functional asymmetry is due to an *endocrine* asymmetry imposed upon the myometrium by the local progesterone effect of the placenta. This theory led to extensive laboratory investigations. Functional asymmetry was demonstrated in the rabbit uterus by a variety of experiments,[7-9, 15, 18, 19] while endocrine asymmetry has been produced experimentally by local intra-amniotic progesterone treatment.[19] These observations are supported by recent studies carried out in pregnant cats.[12]

The experiments to be described provide additional evidence for the endocrine and functional asymmetry of the rabbit uterus in late pregnancy. Unlike women, rabbits are believed to require the progesterone secretion of the corpus luteum throughout the entire duration of gestation.[5] This secretory activity can be completely substituted for by systemic progesterone treatment.[4, 6, 20] However, the notion that pregnancy in rabbits cannot continue without the ovaries and that the rabbit placenta is unable to substitute for ovarian function is challenged by

From the Rockefeller Institute.

recent experiments to be published elsewhere.[11] This observation and the demonstration that placental endocrine function is indispensable for the maintenance of pregnancy[19] are best explained by the assumption that pregnancy in rabbits is maintained by the combined effects on the uterus of a systemic (corpus luteum) and a local (placental) progesterone action.[9, 10, 18, 19] An additive effect, of various proportions, of a systemic and of a local progesterone action can well explain the species differences in the contractility and pharmacologic reactivity of the pregnant uterus. In rabbits the systemic progesterone effect of the corpus luteum seems to dominate the myometrium, whereas in women it is the local effect of the placenta which is dominant. However, in both species progesterone appears to be a key substance in control of the pregnant uterus and the placenta is also an indispensable endocrine organ. This is in keeping with the notion of a common basic regulatory mechanism for the maintenance and termination of gestation.[6, 9, 10]

Methods and results

Mature virgin New Zealand white rabbits were mated under observation. The hour of successful mating was noted and will be referred to as time zero of gestation. In our colony, with a litter of more than 5, delivery usually occurred during the night of the thirty-first day or on the morning of the thirty-second day. Rabbits with a litter of less than 5 usually carried pregnancy for an additional 24 to 48 hours as described by Wishart and Hammond.[25] Prolonged gestation in animals with small litters is an interesting and significant phenomenon which will be described and discussed elsewhere.

Earlier experiments[2, 6, 14] carried out on pregnant rabbits showed that in about 94 per cent of the animals delivery can be induced on the thirty-first day by the intramuscular injection of a single dose of 1.0 I.U. oxytocin, whereas in only 60 per cent was labor inducible at 30 days plus 6 hours after mating. In less than 7 per cent labor could be induced on the twenty-ninth day,

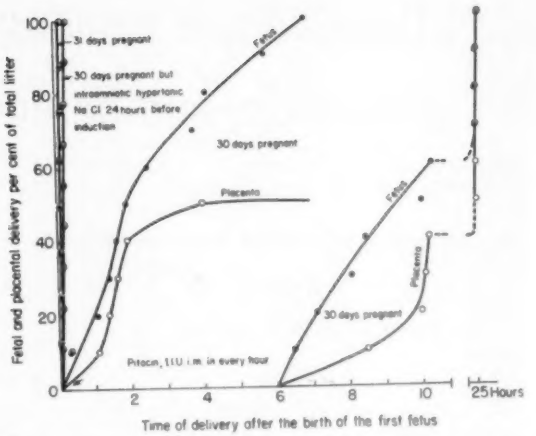


Fig. 1. Fast and slow oxytocin-induced delivery in rabbits.

irrespective of the dose administered (within reasonable limits) or the route of administration. It was concluded from these experiments that in rabbits delivery cannot be induced, as a rule, before the thirtieth day of gestation[6] because a drastic change in the oxytocin response of the rabbit uterus takes place only during the thirtieth day.

On the thirtieth to the thirty-first day, effective progesterone treatment 12 to 24 hours before induction defends the uterus against oxytocin action, and pregnancy is maintained as long as progesterone treatment continues.[6, 14] These observations agree well with the finding that the endocrine condition of the uterus changes 24 to 48 hours before parturition.[1, 6-8, 22, 23] Normal delivery in rabbits at the end of the thirty-first or at the beginning of the thirty-second day is characteristically a fast process. Delivery of the placenta quickly follows the birth of the fetus and there is usually only a trace of bleeding. Labor can be better observed and timed by induction with oxytocin on the morning of the thirty-first day, a treatment which accelerates delivery.

We, therefore, induced labor in a group of rabbits on the morning of the thirty-first day and noted the time of delivery of each fetus and placenta. Fig. 1 (curve *31 days pregnant*) illustrates a characteristic observation. The first fetus was born a few minutes after the intramuscular administration of 1.0 I.U. of oxytocin (at time zero). The placenta

and the rest of the litter were delivered in rapid succession. When the curves of delivery of the fetuses and placentas were drawn on the given time scale only one curve was obtained, since the delivery was so quick as to be completed within 15 minutes. There was no marked bleeding either during or after delivery.

If delivery was induced 24 hours before, i.e., on the morning of the thirtieth day, labor was characteristically different. Fig. 1 gives two examples for the time course of typical induced delivery on the thirtieth day (curves *30 days pregnant*). Following the injection of oxytocin one animal started to deliver within 30 minutes, whereas the other required 6 injections (one every hour) before the first fetus was born. Since the first oxytocin injection seldom brings about the onset of delivery, labor is delayed as a rule. In all instances it is also prolonged, and oxytocin treatment has to be repeated (at one-hour intervals) in order to continue and complete delivery.

The observation of special significance in our present discussion is the fact that fetal and placental delivery followed two independent courses, since delivery of the placentas was greatly delayed (Fig. 1, curves *30 days pregnant*). When all the fetuses had been born some placentas were retained, a striking phenomenon when compared with the normal or oxytocin-induced delivery at term. Furthermore, when oxytocin treatment was interrupted at a time when only half of the litter had been delivered, labor also stopped. A period of 10 to 15 hours without oxytocin treatment was a sufficiently long time for the necessary changes to occur in uterine excitability and pharmacologic reactivity. After such a period the animal was delivered normally and quickly when oxytocin treatment was resumed (Fig. 1, curve, extreme right). Thus, in the 30-day-pregnant rabbit oxytocin induced delayed and prolonged delivery, with placental retention and with marked hemorrhage. Clearly, in the same rabbit one can demonstrate delayed and prolonged labor with placental retention and hemorrhages as well as prompt and quick delivery, depending on the time in gestation when induction is carried out.

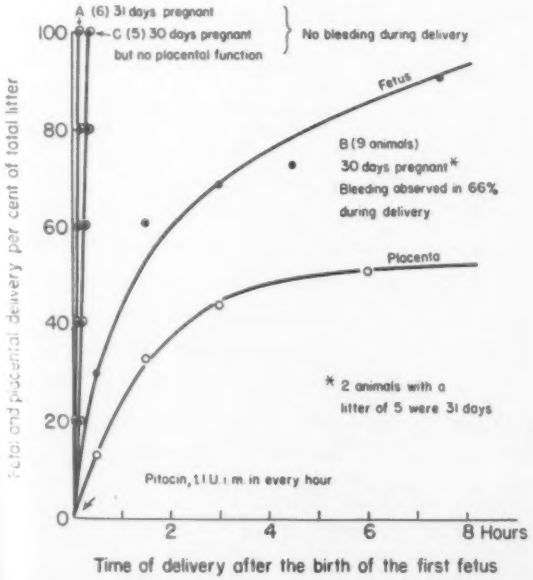


Fig. 2. Fast and slow oxytocin-induced delivery in rabbits.

In the next series of experiments we investigated the relationship between placental function and delayed and prolonged delivery, placental retention, and hemorrhage. The sharp dependence of these abnormalities of labor on the stage of gestation strongly suggests an endocrine background. The fact that the oxytocin effect is suspended or that pregnancy can be prolonged by progesterone (not by estrogen) in the rabbit from which the ovaries have been removed supports this assumption and suggests that progesterone is the hormone involved.

We studied, therefore, the endocrine mechanism underlying this functional asymmetry of the uterus. Hypertonic sodium chloride was injected into the amniotic sacs of pregnant rabbits (1 ml. saturated NaCl per sac) on the twenty-ninth day of gestation. We expected that this treatment would dehydrate the placenta and seriously damage its endocrine function (and, of course, the transport function as well). Such an effect should lead to a gradual withdrawal of the placental block without immediate placental detachment. We also expected that when delivery is induced by oxytocin in such an

animal "normal" delivery would occur, i.e., prompt delivery of both the fetuses and the placentas without marked bleeding. This is what we have found (Fig. 1, curve *30 days pregnant, but with intra-amniotic hypertonic NaCl*).

As a control experiment we studied the effect of placental dislocation on the inducibility of the 30-day-pregnant rabbit. These controls behaved during delivery in the same way as those treated with saturated NaCl. Of course, immediately after placental dislocation the animals bled into the uterine cavity but no marked hemorrhages were observed during labor. As additional controls, we treated rabbits intra-amniotically with physiologic NaCl on the twenty-ninth day of gestation. When delivery was induced in these rabbits 24 hours later they went into the prolonged labor characteristic of the intact 30-day-pregnant rabbits.

Thus the "defense" mechanism of pregnancy is suspended by placental detachment or by the intra-amniotic injection of dehydrating agents on the twenty-ninth day, and labor induced 24 hours later is similar in these animals in spite of the very great difference in the methods by which placental function was altered. The fact that the effect of placental dislocation and intra-amniotic hypertonic NaCl are manifested in inducibility at about the same time strongly suggests that both methods are effective because they lead to the cessation of placental endocrine function. The demonstration that intra-amniotic physiologic NaCl is ineffective shows that the intra-amniotic manipulation of this type in itself, does not affect the maintenance of pregnancy. The fact that alterations in placental function lead to the withdrawal of the defense mechanism of pregnancy and that this withdrawal permits an early induction of labor and also that parturition itself is of short duration is of considerable theoretic and practical significance.

Fig. 2 summarizes our experiments on 20 animals. The differences in behavior between the various groups of pregnant rabbits are very marked and consistent. The following comments need to be made concerning Fig. 2.

Since the 30-day-pregnant rabbits respond to repeated oxytocin injections with a delay of different extent, the time when the first fetus is born was taken as the beginning of labor and the delay in the oxytocin response was not indicated on the graph. Thus, the curves for fetal and placental births describe the average length of labor after the delivery of the first fetus without indicating the delay in the onset of labor. The fact that we observed marked bleeding in only 66 per cent of the cases does not exclude the possibility of hemorrhages in the remaining 34 per cent of these animals, for at the beginning of our study we did not specifically look for hemorrhages since marked bleeding does not accompany normal delivery in rabbits.

In the last group, 3 animals were treated with saturated NaCl intra-amniotically, and in 2 animals the placentas were dislocated, after laparotomy, by gentle pressure against the placental bed. Two of the animals with small litters behaved on the thirty-first day like 30-day-pregnant animals. This agrees closely with Wishart and Hammond's[25] finding and with our own observation that animals with a small litter are about 24 to 48 hours "behind time" with respect to the onset of delivery.

Comment

In rabbits, spontaneous labor is characteristically quick and fetuses and placentas are delivered in rapid succession, without marked bleeding during or after parturition. In order to expose some anomalies of human labor to experimental study we induced delivery prematurely in rabbits and observed delayed and prolonged labor, placental retention, and hemorrhages. Delivery was abnormal in spite of uterine activity adequate for the full dilatation of the cervix and for the delivery of the first fetus. We demonstrated that quick delivery can also be induced prematurely, with oxytocin, if placental function is suspended 24 hours before induction.

It is significant that this demonstration was made in rabbits, a species in which the maintenance of pregnancy is thought to depend entirely on corpus luteum function rather than on placental endocrine control.

We believe that in rabbits pregnancy is maintained largely by the systemic progesterone effect of the corpus luteum aided and substantiated by the local effect of the placenta. The ovarian progesterone reaches the uterine muscle via the systemic circulation, providing the uterus with a diffuse block. As long as this block is sufficiently strong labor cannot be induced by oxytocin. It is demonstrated that labor cannot, as a rule, be induced in rabbits before the thirtieth day of gestation.

When the systemic block becomes ineffective during the thirtieth day of gestation oxytocin promotes uterine activity to an extent sufficient to expel the fetus. Because of the auxiliary local effect of the placenta, the block at the placental portions is maintained while it is withdrawn at the interplacental portions. During this transient endocrine condition induction leads to delayed and prolonged delivery and placental retention. Since the endocrine condition of the uterus is in a transient state, the time course of fetal and placental birth shows considerable variation.

Bleeding during parturition may be expected if some of the placentas separate either partially or completely and sustained shortening of the muscle fibers at the placental bed is delayed because of a partial block. The experimental fact is that for a number of hours during the thirtieth day of pregnancy there is marked bleeding during delivery. Fetal and placental delivery follow two distinct time courses indicating that the placental bed responds to oxytocin at a later time than the rest of the myometrium. These observations are best explained by a functional asymmetry of the rabbit uterus in late pregnancy.

Suspension of placental function results in quick delivery. This effect may be explained by the dependence of corpus luteum function on placental estrogen.[16] However, such a relationship between the placenta and the corpus luteum does not explain the local effect of the placenta on the propagated activity of the placental bed, nor does it explain placental retention when premature delivery is induced. The simplest interpretation of the present observations is that the placenta exerts a local effect on the placental bed mediated by progesterone. Previous observations[19] suggested that the placenta may produce about one fourth of the total progesterone in rabbits in the late stages of pregnancy. If so, this auxiliary placental progesterone could play a decisive role in the termination of pregnancy and in the control of placental attachment.

Our more recent experiments, to be published elsewhere, offer additional support for a placental progesterone production in rabbits in late pregnancy.[11]

The functional inhomogeneity of the 30-day-pregnant rabbit uterus is interesting for it can be compared with the functional asymmetry shown by the pregnant human uterus in the selective delivery of the fetus and the placenta or one fetus of a pair of twins. Functional asymmetry can arise from a concentration gradient of progesterone in the uterine wall with a peak at the placental bed. An endocrine asymmetry could provide the human uterus with properties allowing variations in the normal course of labor. With increasing fetal growth, uterine portions far away from the placenta may become partially unblocked. These areas would then become spontaneously active and pharmacologically reactive and it is likely that this localized activity was recorded in women not yet at term by Caldeyro-Barcia and Poseiro.[3]

Endocrine and functional asymmetry at an early stage of human pregnancy can also account for the differences between women and rabbits in the oxytocin response and in the relative success of inducing premature labor in women, for in rabbits activity is suppressed until the twenty-ninth day of pregnancy by the largely systemic control of the corpus luteum. Asymmetrical uterine activity can also explain the different find-

ings concerning the oxytocin response of the human uterus in late pregnancy, because the different methods used for recording "uterine activity" reveal partial activity to a greater or lesser extent.

Another point brought out by these observations is relevant to the significant problem of the relative importance of cervical resistance in the course of delivery. In contrast to women, rabbits do not possess a structurally well-developed cervix, yet their oxytocin-induced premature delivery is greatly delayed and prolonged. When during induced premature delivery the rabbit cervix yields to the expulsive forces delivering the first fetus, the cervical resistance is clearly overcome. However, labor will stop if it is not forced to continue by repeated oxytocin injections, and it is prolonged for several hours in spite of the open cervix and of sustained oxytocin stimulation. It appears, therefore, that slow progress and prolonged labor result primarily from the "type" of uterine activity superimposed on the cervix rather than on the properties of the cervix itself. Also, it seems that the type of uterine activity is under endocrine control.

Prolonged labor is best explained by a functional inhomogeneity resulting from partial activity coincidental with inactivity. The functional asymmetry of the human uterus is not obvious, however. Thus, when clinical labor is accompanied by lack of progress, it is customary to assume a primary failure of the cervix to ripen. We suggest that the cervix is not responsible for the lack of progress, but slow effacement and dilatation are clinical symptoms of an abnormal type of uterine activity which is an important causative factor in prolonged labor.

The location of the placenta in the uterine cavity may be one factor in determining the type of activity of the uterus. At present there is no method which at an early phase of parturition can *clearly* and unequivocally distinguish between effective and ineffective uterine activity, and reliably predict the progress of labor. However, a clear distinction could perhaps be made if a method were developed which would topographically describe the functional asymmetry of the uterus in each individual case.

Prematurely induced delivery of the 30-day-pregnant rabbit is of interest for it suggests new aspects in the study of abnormal human labor. The proposed common basic mechanism in rabbits and women underlying normal delivery as well as delayed and prolonged labor, placental retention, and hemorrhages is, of course, no more than a working hypothesis. It might be rewarding, however, to inquire through carefully controlled clinical trials whether this hypothesis has merits.

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To do or not to do—a critical review of vaginal examination during labor

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VAGINAL examinations during labor have long been taboo in American hospitals. Everyone is familiar with the time-honored arguments against vaginal examinations, and they will not be repeated here. Kroenig[4] in 1893 first advocated rectal examinations in Germany. Their popularity soon spread to this country. Prior to this vaginal examinations were widely used. Semmelweis[8] in 1847 investigated puerperal infection in Vienna and concluded that it was caused by the introduction of septic material into the birth canal by the examining hand of the obstetrical attendant. Eastman[2] suggests performing vaginal examinations only for special reasons, and then only after somewhat elaborate preparations of both the patient and examiner.

Periodically, all medical concepts must be re-evaluated if we are to maintain ourselves in the dynamic world of medicine. It was inevitable that someone would question the relative safety of vaginal examinations in labor. In 1924, Ralph Reis[6] reviewed the European literature and noted a greater incidence of puerperal infection in those patients who were examined vaginally. However, in a comparative study of patients in Michael Reese Hospital who were examined vaginally and rectally, he found no essential difference in the incidence of postpartum temperature elevation. He emphasized that as the number of vaginal examinations increased from only 1 to 2 or more the number of patients in the afebrile category markedly decreased. Prystowsky[5] in 1954 and Schaefer and associates[7] in 1956 reported similar findings in comparative studies. Bishop[1] advocated routine office vaginal examinations for all prenatal patients in the last month of gestation. In a series of 6,000 office vaginal examinations on 2,000 patients, he reported an incidence of 2.0 per cent morbidity. He concluded his paper by saying that vaginal examinations should be an "integral and routine part of prenatal care."

With these concepts in mind it was decided to evaluate a series of patients who would routinely be examined vaginally in the clinic from the thirty-sixth week to term and who would be followed in labor by vaginal examinations.

Methods and results

For the purpose of this paper the standard definition of puerperal morbidity was used, i.e., a temperature of 100.4° F. on any 2 of the first 10 postpartum days with the first 24 hours post partum being excluded. Patients with temperatures of 100° F. to 100.4° F. were also evaluated and included in this study. A total of 475 patients comprise the group. All were examined vaginally during labor and in the clinic during their last month. Examinations performed in the clinic were done with autoclaved, but not necessarily sterile, gloves. No perineal antiseptics were used. The labia were separated with one hand and one or sometimes two gloved fingers explored the vagina. Patients ad-

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The contents herein reflect the personal views of the author and are not to be construed as a statement of official Air Force policy.

mitted to the labor rooms received routine perineal preparation. Vaginal examinations were done with sterile gloves. There was no surgical cleansing or washing of the examiners' hands. The labia were separated and a solution of aqueous benzalkonium was poured over the perineum and into the vagina. The only exceptions to the above routine were patients with vaginal bleeding. In these cases the usual procedure of sterile examination in the "set-up" delivery room was used. No cases of placenta previa occurred in this study.

A total of 5,450 vaginal examinations were done, with 4,025 during labor and 1,425 in the clinic. The average age of the patients studied was 23 years. Most patients remained in the hospital for 5 days. Both primiparas and multiparas were included. The average length of labor was 5.5 hours. The average patient was examined 8.5 times during labor and 3 times in the clinic prior to the onset of labor.

There were 10 patients classified in the puerperal morbidity group. Twenty-nine had temperatures between 100 and 100.4° F. Table I gives the distribution of parity in both groups. All 10 patients in the puerperal morbidity classification required episiotomies. An attempt was made to correlate temperature elevation with the number of examinations, but the average number of examinations in the morbidity group was essentially the same as the entire series, i.e., 8.2. However, 10.8 examinations per patient were performed in the group with temperatures above 100° F. but not exceeding 100.4° F. It was also noted that the average length of labor in the febrile patients was longer than that in those that remained afebrile. A labor of 8.7 hours in the puerperal morbidity patients and 7.8 hours in the 100 to 100.4° F. patients was found. Table II is a tabulation of the above data.

Comment

Although no control group of patients examined rectally during labor is included, a review of the literature[1, 3, 5-7] furnishes ample comparable material. A maternal morbidity rate of 2.1 per cent in this study is almost identical to the 2.5 per cent found by Fara and associates[3] in 1956. If the entire group of patients with temperatures above 100° F. is included, the morbidity in this study is 8.2 per cent. Prystowsky[5] was able to determine a rate of 10.3 per cent in a similar group of patients examined vaginally and a rate of 10.4 per cent in a group examined rectally. His study totaled 697 patients. Fara[3] found almost identical results in temperature elevations above 100° F. when comparing vaginal and rectal examinations in a total of 1,535 patients, i.e., 12.9 per cent versus 12.8 per cent.

It is noteworthy that with an increase in the length of labor there is an increase in temperature elevations. There is a similar increase in the number of vaginal examinations during this prolonged period of labor. No correlation can be found between the amount of temperature elevation and the number of examinations since the group with temperatures of 100.4° F. or above were examined 8.2 times and the entire group 8.4 times. The presence or absence of an episi-

Table I

Parity	*No. of patients with temperature 100.4° F. or more*	*No. of patients with temperature 100° to 100.4° F.*
0	7	15
1	1	4
2	1	6
3	1	1
4	0	2
5	0	1
Total	10	29

Table II

Class	*Patients with temperature 100.4° F. or more*	*Patients with temperature 100 to 100.4° F.*
Episiotomy	10	26
Average no. examinations	8.2	10.8
Average length labor	8.7 hours	7.8 hours
Total morbidity	2.1 per cent	
Total febrile	8.2 per cent	

otomy did not appear to influence the morbidity in this study. One can postulate that with prolonged labor and increased vaginal examinations the probability of introducing pathogenic organisms into the birth canal increases. Whether the bodily defenses react in such a manner to produce a temperature elevation of 100° F. or greater than 100.4° F. may be an individual variation. It does seem conclusive that an increased number of examinations is more likely to produce some degree of febrile response. This confirms the observation of Reis[6] in 1924.

The patients in this study readily accepted vaginal examinations during labor. This examination is less uncomfortable than the time-honored rectal. Prystowsky[5] concluded that the danger of vaginal examinations in labor were overestimated. The present study confirms this finding. I do not advocate routine vaginal examinations in labor to be performed by all doctors. A careful vaginal examination by trained, experienced hands can be a safe and extremely informative procedure.

Summary and conclusions

An analysis of the febrile response of 475 parturients was made following the employment of vaginal examinations before and during labor. No surgical cleansing or washing of the examiners' hands was done during labor; however, sterile gloves were used. A total of 5,450 vaginal examinations were done. A maternal morbidity rate of 2.1 per cent was found. This morbidity rate compares favorably with the rates determined in hospitals where rectal examinations are routinely employed. If properly used, vaginal examination can be a safe and very informative procedure.

We wish to thank Lt. J. DeCell, Lt. J. Crawford, and staff without whose help this paper would not have been written.

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Liquor amnii analysis in the management of the pregnancy complicated by rhesus sensitization

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ALTHOUGH the routine induction of premature labor in rhesus sensitized patients must be condemned,[8, 13, 16a] selective premature delivery obviously has much to offer, not only in the prevention of stillbirth,[16] but also in the avoidance of the severely anemic and moribund neonate. To practice selective induction, the obstetrician requires a reliable assessment of the condition of the baby in utero and warning of the potential intrauterine death in order that the best compromise between prematurity and anemia may be achieved.

The controversy which surrounds the role of serologic data in providing this guidance in the individual patient has been recently summarized.[11]

Bevis[4-7] has shown that the liquor amnii presents diagnostic features in hemolytic disease. Bevis[5] demonstrated a correlation between the cord hemoglobin level of the baby and the nonhematin iron concentration in liquor but obtained this relationship by taking the highest value encountered in a series of samples. This proviso was omitted from a later publication[6] but is a point of practical importance since it complicates the assessment for both doctor and patient. Bevis[6, 7] also showed that by estimating the bilirubin and oxyhemoglobin content of liquor, either biochemically or spectrophotometrically, it was possible to detect babies in whom kernicterus was likely to develop. However, this information could be obtained alternatively from cord serum at birth. The need for exchange transfusion for the prevention of kernicterus may be gauged from the subsequent behavior of the serum bilirubin level.[9, 21]

Walker[17] examined the spectral absorption curves of liquor specimens from 101 rhesus sensitized patients. He claimed that it was possible to predict which babies were affected by hemolytic disease provided the specimens were fresh and obtained before the thirty-fifth week, but he gave little guide to the practical application of this information in the management of the individual patient.

The present report describes the spectrophotometric findings in liquor specimens from 101 rhesus sensitized pregnancies in the National Women's Hospital, Auckland, and suggests a manner in which these findings may be used with precision in selecting the optimal time for delivery.

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Methods

Samples of liquor were obtained by abdominal amniocentesis[12, 14, 15, 20] or at surgical induction of labor.

Spectral absorption curve. Specimens were tested fresh if possible; otherwise, they were protected from light and refrigerated. Specimens were centrifuged free of vernix, squamous debris, and any erythrocytes. They were examined in 1 cm. light path glass or silica cuvettes in a Unicam SP600 or SP500 spectrophotometer.

Normally the examination was made on undiluted liquor but occasionally heavily pigmented fluid required a two-, four-, or eightfold dilution with distilled water. Opti-

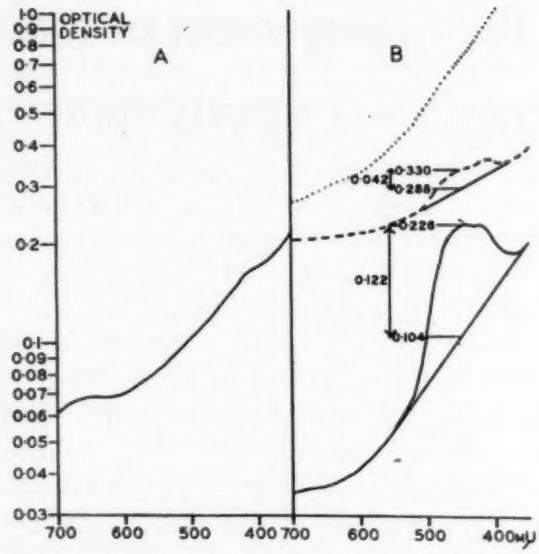


Fig. 1. *A*, "Negative" curve. Spectral absorption curve of liquor at 35 weeks from a rhesus sensitized patient but with an unaffected baby. *B*, "Positive" curves. Absorption curves of liquor at 31 weeks (solid line), 35½ weeks (dashed line), and 38 weeks (dotted line) from a pregnancy yielding an affected baby with a cord hemoglobin of 13 Gm. per 100 ml. at 38 weeks. The method of measuring the 450 mμ peak is illustrated.

cal density was plotted on a logarithmic scale against wave length[7, 17] (Fig. 1). Experience showed that a reliable outline of the spectral absorption curve could be obtained by readings at the following wave lengths: 350, 365, 380, 390, 400, 410, 415, 420, 430, 440, 450, 460, 470, 485, 500, 515, 530, 540, 555, 570, 585, 600, 620, 640, 670, and 700 mμ. Certainly, in many specimens, far fewer points would have sufficed to define the curve but in any single instance it was only after the curve had been drawn and not before that it was possible to decide which points were superfluous.

Nonhemin iron estimation. The nonhemin iron content of liquor was measured by a phenanthrolene method modified from the procedures described by Kaldor[10] and Barkan and Walker[3] for serum iron. Deionized distilled water was used for making up the solutions and in the blank. Although the concentration of proteins in liquor is much lower than in serum, precipitation was easy in the great majority of specimens. Occasionally, however, in unpigmented specimens of liquor only, 20 per cent trichloracetic acid left a persistent opalescence which could not be cleared by prolonged centrifuging or filtration. Since this phenomenon was observed only in liquor from unaffected or very mildly affected infants it was not an inconvenience in practice (Fig. 10).

Blood specimens. Although a blood-free sample of liquor was the goal in amniocentesis, any blood specimens encountered during the puncture were carefully collected. Such specimens together with any erythrocyte film in the centrifuged deposit from liquor were screened for fetal or maternal origin by a modification of the method of Apt and Downie.[2] The dose of alkali had been dried in corked, wax-sealed tubes. A fetal (alkali resistant) reaction was then confirmed by the presence of nucleated red cells in a stained film and the ABO and D type and direct Coombs reaction of the cells were determined.

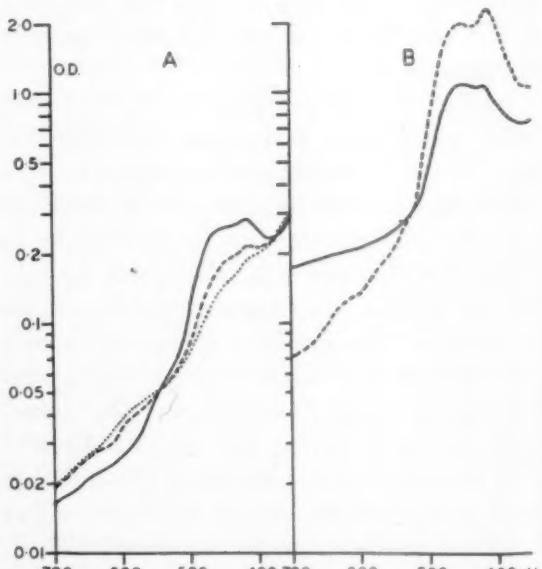


Fig. 2. *A*, The effect of light on the spectral absorption curve of liquor. Solid line = specimen refrigerated for 9 months in darkness. Dashed and dotted lines = the same specimen after exposure to winter sunlight for 15 and 30 minutes, respectively. *B*, Simultaneous curves of liquor (solid line) and fetal serum (dashed line) at 28½ weeks with a severely affected fetus.

Results

Spectral absorption curves of liquor. The characteristic features of liquor in hemolytic disease, as described by Bevis[7] and Walker,[17] have been confirmed. Whereas the spectral absorption curve of normal liquor was approximately a straight line from about 365 mμ to 550 or 600 mμ, in hemolytic disease, there was a deviation or peak centered on 450 mμ and a less consistent peak on 415 mμ (Fig. 1) which Bevis[7] attributes, respectively, to bilirubin and oxyhemoglobin. However, it was observed that the spectral absorption curve of normal liquor was rarely as linear as the late pregnancy example shown in Fig. 1, *A*. At 28 to 33 weeks, normal liquor frequently showed a conspicuous bulge or peak on 450 mμ (Fig. 6, *B*). Hence, it was necessary to measure the 450 mμ peak and establish limits of normality in terms of maturity. Several simple precautions were found to be necessary in this investigation.

First, the specimens had to be protected from light promptly. It was observed that the pigment peaks had a half life of about 10 hours in laboratory daylight and 12 to 18 minutes in winter sunlight (Fig. 2, *A*). By contrast, no significant change was seen in the sterile specimens stored in the dark after 9 months refrigeration or 30 days at room temperature.

Second, it was necessary to recognize any contamination of a specimen by fetal blood since the pigments have been shown[7] (Fig. 2, *B*) to be present in much higher concentration in fetal serum than in liquor (Fig. 4).

A third potential difficulty, not encountered in the present series, concerned the patient with a history of antepartum hemorrhage. Specimens of liquor obtained at amniography from such patients usually showed no abnormality. A number, however, were stained with free maternal hemoglobin while in 2 cases suspiciously large peaks on 450 mμ were found and in one case a definitely abnormal peak was encountered (Fig. 3, *A*).

These observations suggested that the degradation of any substantial volume of intrauterine blood—retrochorionic and retroplacental, as well as fetal—could produce the characteristic pigmentation of liquor. Had these rare patients with antepartum hemorrhage been also rhesus sensitized, a false diagnosis of hemolytic disease in the infant could have been made.

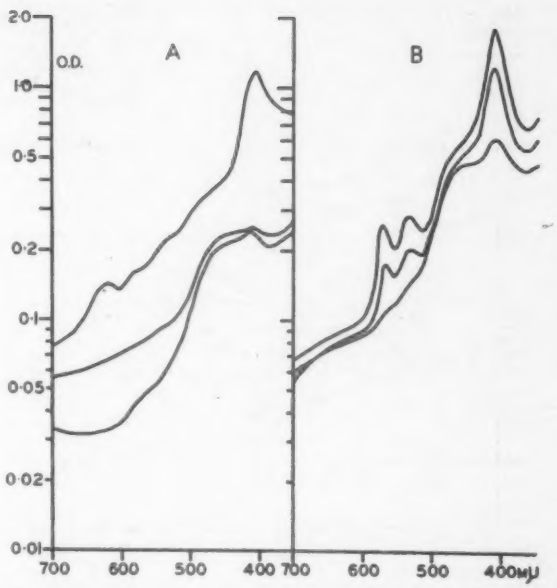


Fig. 3. *A*, Spectral absorption curves of liquor from patients with antepartum hemorrhage. Upper curve = absorption bands of oxyhemoglobin and methemalbumin in liquor at 28 weeks from a patient with repeated hemorrhages from a placenta previa. Middle curve = abnormally large peak on 450 mμ at 34 weeks from a patient with placenta previa and placenta accreta. Lower curve = suspiciously large peak on 450 mμ at 29 weeks from a patient with repeated marginal hemorrhage from a cornual implantation. *B*, The distortion of the 450 mμ peak by increasing contamination with free oxyhemoglobin.

Since in both liquor from unaffected babies in late pregnancy and light-exposed liquor from affected babies, the spectral absorption curve was approximately linear over the range 365 to 550 mμ, the optical density of the peak at 450 mμ was measured from a base line drawn tangentially to the curve at approximately these points (Fig. 1, *B*). A little care was necessary in the presence of free oxyhemoglobin which was sometimes a genuine fetal liquor constituent but more frequently an artefact from hemolysis of a few contaminating maternal or fetal erythrocytes. The small peaks of oxyhemoglobin at 540 and 575 mμ interrupting the

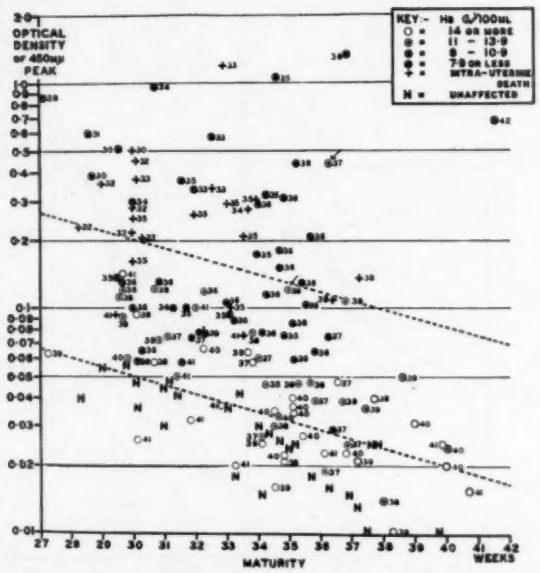


Fig. 4. The significance of the 450 mμ peaks recorded at different maturities. The symbols represent the ultimate condition or fate of the babies, the attendant numbers, the week in which delivery or intrauterine death occurred. Note that week 28 begins at 27 weeks, 1 day, and ends at 28 weeks. The two arrows indicate peaks augmented by contamination with fetal serum. The zones separated by the dotted lines are explained in the text.

curve meant that the usual smooth sweep in this region had to be estimated by eye for the tangent to be drawn but this presented little difficulty. However, the more striking peak of oxyhemoglobin on 415 mμ although sharp could still add to the absorption at 450 mμ if large (Fig. 3, *B*). In part this error was compensated by a corresponding addition over the 350 to 380 mμ range which thus elevated the base line. Experimental contamination suggested that the remaining error could be reckoned as 5 per cent of specific optical density of the 415 mμ oxyhemoglobin peak.

Examination of numbers of specimens of liquor from sensitized patients but with unaffected babies showed that the 450 mμ peak or bulge always diminished with increasing maturity (Figs. 5 and 6, *B*). A similar shrinkage was observed in specimens from many affected babies. When the affliction was mild, the size of the peak and the rate of shrinkage could not be distinguished from the values for unaffected babies.

With increasing severity of hemolytic disease, the pigment peaks were significantly larger at all stages of maturity but now it was seen that some peaks remained stationary or increased with maturity. This behavior was associated with severe affliction which also was seen with large peaks even though shrinking. This variation suggested differing times of onset and course of development of hemolytic disease in individual babies. It is of interest that, in the last trimester, no peak which was shrinking subsequently increased in size and, conversely, no peak which grew with maturity subsequently showed any significant shrinkage. The individual analyses of all specimens from all pregnancies are shown in Fig. 4,

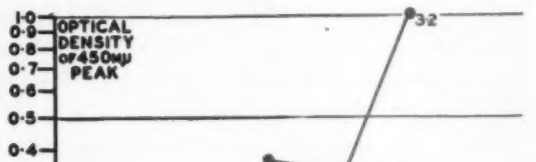


Fig. 5. Examples of the behavior of the 450 mμ peak in 20 pregnancies and the clinical results. The upper figure of each pair indicates cord hemoglobin in grams per 100 ml.; the lower figure, maturity at delivery in weeks and days (omitted where the hemoglobin value is simultaneous with the pigment peak). With intrauterine death, the maturity at that event is recorded. The convention of symbols is the same as for Fig. 4. The solid lines connect succeeding points in the same pregnancy and do not imply the (unknown) intermediate values.

where the size of the pigment peak at the maturity at which it was observed is related to the severity of the affliction at the maturity of delivery. Where intrauterine death resulted, the maturity at this occurrence rather than delivery is shown. It must be noted that, since Fig. 4 includes many instances of repeated sampling, the points gathered in any one area do not represent the frequency distribution of the given outcomes. Rather they provide some examples of the potential fates which babies with pigment peaks of that size at that maturity can meet. Examples of the behavior of the 450 mμ peak in individual pregnancies are shown in Fig. 5. It was found that the severity of the hemolytic disease could be predicted by considering the size and trend of the 450 mμ peak in liquor in relation to 3 zones which are shown in Figs. 4 and 5.

Peaks landing in the bottom zone were associated with unaffected babies or affected babies in whom the affliction was very mild. These 2 situations were indistinguishable. All peaks in this zone diminished in size with increasing maturity.

Peaks in the top zone represented very severely affected babies whenever discovered and, with very few exceptions, intrauterine death was imminent.

The behavior of peaks located in the mid-zone early in the third trimester was more complex. Some shrank rapidly and passed into the bottom zone. This course was associated with mild hemolytic disease. Others remained stable or increased in size so that they approached or entered the top zone. This behavior was associated with severe anemia. Since a few of these peaks which grew alarmingly appeared quite innocent early in the third trimester (Figs. 5 and 6, *A*), the lower boundary of the mid-zone (Figs. 4 and 5) was placed low enough to include them rather than high enough to exclude all unaffected babies. A third group of mid-zone peaks diminished but followed a course parallel to the boundaries. The nearer this course lay to the upper boundary the more severely were the babies affected.

As a result of this sorting out of mid-zone peaks, beyond about the thirty-fifth week there was now a fairly continuous gradation from unaffected or mildly affected babies at the bottom of the graph to severely anemic babies at the top (Figs. 4 and 5).

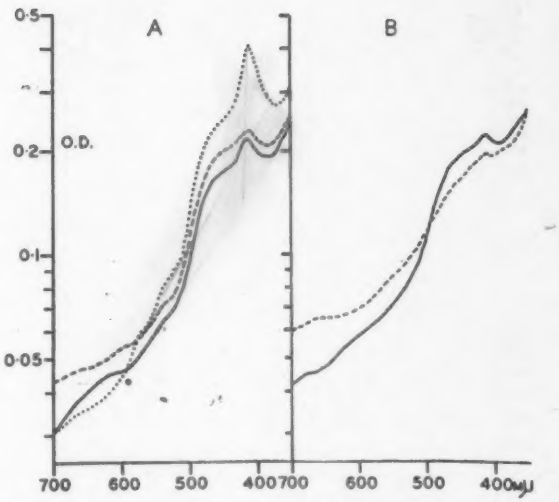


Fig. 6. The progress of 2 peaks of identical size early in the third trimester. *A*, 30 weeks, 1 day (solid line), 34 weeks, 1 day (dashed line), and 35 weeks, 4 days (dotted line). The latter specimen was obtained at surgical induction. The baby, the firstborn of a patient sensitized by transfusion, had a cord hemoglobin of 9.9 Gm. per 100 ml. *B*, 29 weeks, 6 days (solid line), and 35 weeks (dashed line). The baby, born at 40 weeks, 5 days was unaffected. These two pregnancies are included in the examples of Fig. 5.

This correlation could also be shown by plotting the cord hemoglobin level against the size of the 450 mμ peak within one week of delivery (Fig. 7). This graph largely, but not entirely, ignores the trends of the peaks with maturity since the less anemic babies were delivered later than those severely affected. In this respect, Fig. 7 approximates to the distribution of hemoglobin levels along a diagonal line from the top left to the bottom right of Fig. 4. Even under these conditions, it is seen from the value of the correlation coefficient that variation in the optical density of the 450 mμ peak or rather its logarithm explained 75 per cent of the variation in cord hemoglobin level within one week. This good agreement was surprising in view of the poor correlation between cord hemoglobin and cord bilirubin

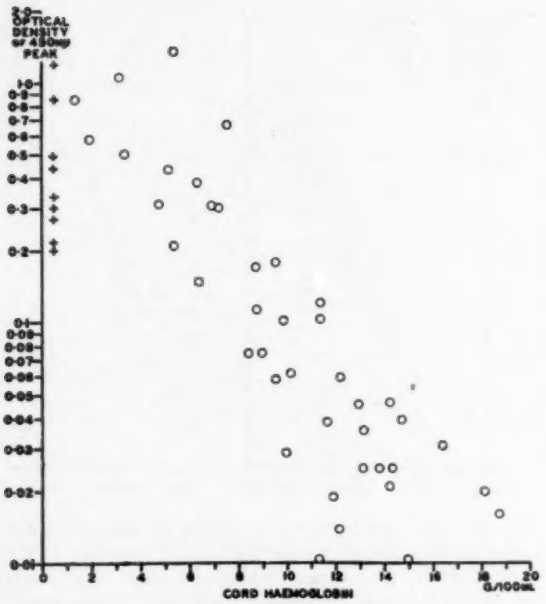


Fig. 7. The relationship between cord hemoglobin levels and the size of the 450 mμ peak recorded within one week. Product moment correlation coefficient, $r = -0.87$, student's $t = 10.9$, $f = 39$, $p <<< 0.001$. The regression line for cord hemoglobin (grams per 100 ml.) on the logarithm of the optical density of the 450 mμ peak is given by $Hb = 22.3 - 6.3 \log_{10}$ (O.D. of 450 mμ peak $\times$ 1,000) $\pm$ 4.2 (= 2 SE).

levels at delivery (Fig. 8) and the even poorer relationship between the size of the 450 mμ peak and the cord bilirubin level recorded within one week (Fig. 9).

In addition to the severity of anemia, the number of exchange transfusions necessary for the control of hyperbilirubinemia also showed some trend with the optical density of the 450 mμ peak. The influence of prematurity was stronger, but exceptions were so numerous that even when both of these factors were taken into account it was not possible to give any useful prediction of the behavior of the bilirubin level in the neonatal period. Some severely affected babies at 35 weeks needed only 2 exchange transfusions while an occasional mildly affected baby at term needed 3.

The presence of peaks due to oxyhemoglobin was not found to have any prognostic value. Certainly hemolysis of any contaminating erythrocytes commonly provided such peaks as artefacts, especially in specimens of liquor obtained at artificial rupture of the membranes. However, considering only

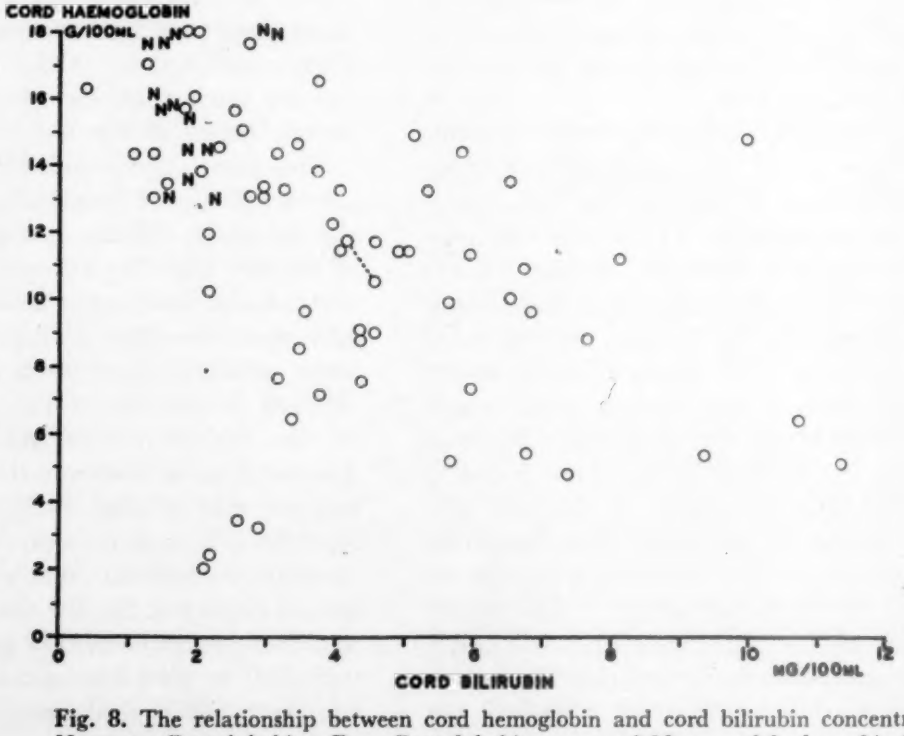


Fig. 8. The relationship between cord hemoglobin and cord bilirubin concentration. N = unaffected babies. For affected babies, $r = -0.38$, $t = 3.2$, $f = 64$, $0.01 > p > 0.001$. The dotted line connects a pair of monochorionic twins.

blood-free specimens where the free oxyhemoglobin was of the fetal type, the 415 mμ peak bore little relationship to either the severity of anemia or the clinical course of the neonate.

Methemalbumin, appearing as a step or peak in the curve about 625 to 630 mμ, was a usual finding in the presence of intrauterine death or a moribund fetus but added little to the information given by the size of the 450 mμ peak.

Meconium stained liquor was encountered only once. This was at surgical induction at term of a patient who had clear liquor at 34 weeks. The baby had a small exomphalos and a congenital heart defect. This apparent association between fetal abnormality and meconium staining of liquor in the patient not in labor had already been noticed in specimens obtained at amniography.

Liquor nonhemin iron content. When the baby was unaffected or only mildly affected by hemolytic disease, the nonhemin iron content of liquor lay in the range 8 to 30 μg per 100 ml. However, moderate and even severe affliction could be associated with these low levels and, while any value over 40 μg per 100 ml. indicated severe anemia, the converse was not true (Fig. 10). Serial estimations showed that the iron level could increase very rapidly, from 20 to 200 or 300 μg per 100 ml. in the space of 3 or 4 days. While such an increase was an ominous sign which justified prompt delivery, in general neither the absolute value of the nonhemin iron nor the trend in repeated sampling provided as much guidance as the 450 mμ peak to the condition and prognosis of the baby.

Fetal blood. In 9 of the 101 pregnant women of this series, a small quantity of fetal blood was aspirated from a vessel in an anteriorly situated placenta. This aspiration occurred more frequently with moderately and severely affected babies where the placenta was bulky but it should be noted also that amniocentesis was performed more often in this group. Because of clotting and the possibility of dilution with liquor, no attempt was made to estimate the hemoglobin concentration of these small specimens. However, the ABO and D type and direct Coombs reaction of the cells were determined. The detection of fetal erythrocytes gave warning of the possibility of fetal exsanguination but no baby came to harm from this encounter[12] or exhibited tachycardia within the next few hours. More important, the detection of fetal cells, especially if intimately mixed with liquor, indicated caution in the interpretation of large pigment peaks (Figs. 2, *B* and 4).

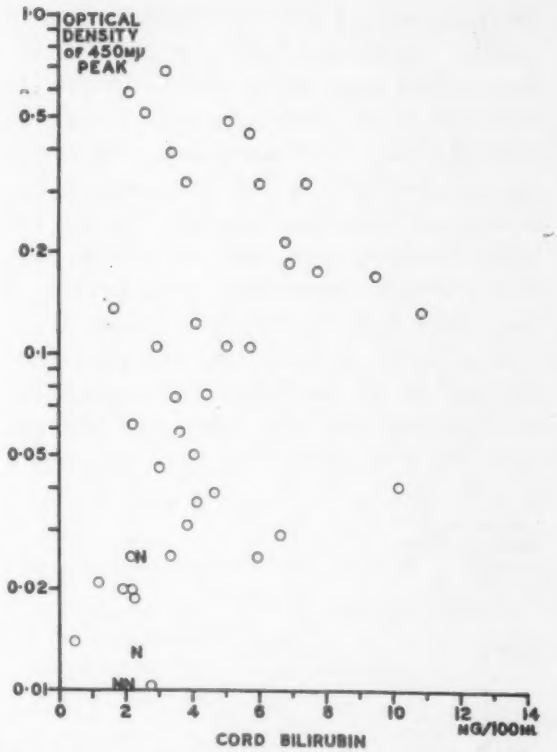


Fig. 9. The relationship between cord bilirubin levels and the size of the 450 mμ peak recorded within one week. N = unaffected babies. For affected babies, the cord bilirubin concentration shows a better correlation with the logarithm of the peak size ($r = +0.29$, $t = 1.82$, $f = 37$, $0.1 > p > 0.05$) than with the natural value ($r = +0.06$, $t = 0.39$, $p > 0.5$).

The antenatal testing of fetal erythrocytes could provide forewarning of the type of blood the baby would need and, most usefully, on occasions vindicated the liquor findings where these were at variance with the expectation from the behavior of the antibody titer and the past history.

Clinical application. For approximately

the first half of this investigation, amniocentesis was limited largely to patients who had already had one or more stillbirths or neonatal deaths from hemolytic disease or at least a severely affected baby. The reason for this selection was that in this group premature delivery was the last resort. The liquor findings were used to confirm that the fetus was indeed affected, especially if the father was suspected or known to be heterozygous, in order that the premature delivery of an unaffected baby might be avoided. Provided the fetus was affected, induction was planned for approximately 2 weeks earlier than the maturity of the last stillbirth or delivery of a severely affected infant.

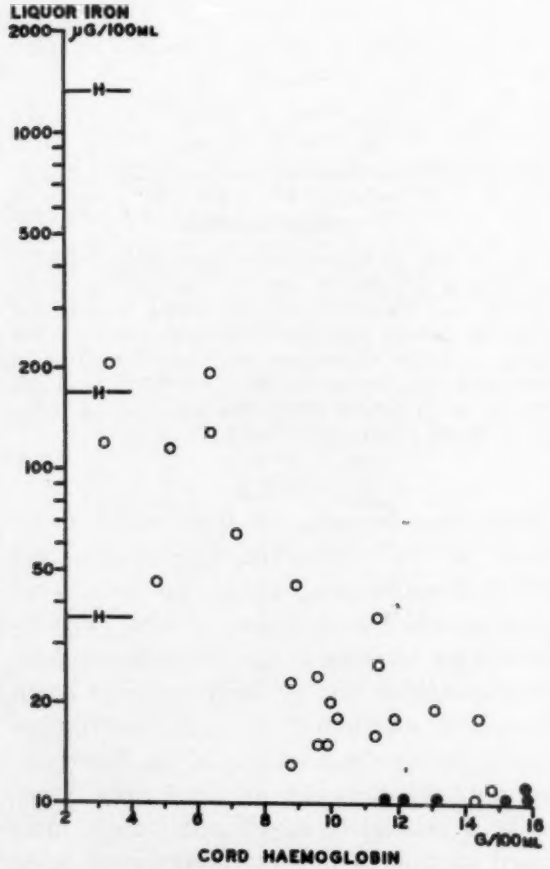


Fig. 10. The relationship between cord hemoglobin levels in affected babies and the nonhemin iron concentration of liquor recorded within 3 days. Filled circles along the abscissa represent estimations complicated by persistent opalescence. Crosses indicate intrauterine death and *H* represents hydropic, moribund neonates. For the remaining points, $r = -0.82$, $t = 6.6$, $f = 21$, $p << 0.001$. The regression equation for hemoglobin (grams per 100 ml.) on iron content (μg per 100 ml.) is given by $Hb = 19.6 - 6.8 \log_{10} Fe \pm 3.7$ (2 SE).

The information sought from the liquor was relatively easy to provide since a single specimen at about 33 to 36 weeks usually could discriminate clearly between an unaffected and a severely affected baby. From a clinical standpoint, however, the results of this policy were often very discouraging. If the liquor was negative, intervention was unnecessary and, if the liquor was positive, intervention was of no avail since the prognosis was often hopeless in either the uterus or the cot. However, the observation that in National Women's Hospital during the period 1949 to 1959 one third of all stillbirths due to hemolytic disease were in first *known* affected babies led to a new policy, especially as confidence grew in the predictions from liquor analysis.

By this scheme, all patients in whom antibodies were found either at the routine initial screening at 12 to 16 weeks or later were subjected to amniocentesis. The first tap was planned for about 29 to 32 weeks. This initial test was used first to detect the very severely affected babies for whom delivery at 32 or 33 weeks could offer a small but definite chance of survival and, second, in other patients to provide a reference point against which subsequent tests could be assessed. In retrospect, this early test could also have been used to dismiss the prospective unaffected or possibly mildly affected babies, but as a precaution during the collection of data many of this group were retested.

The second amniocentesis was carried out between 33 and 35 weeks, the exact time depending on the timing and results of the first test. The usual interval was 2 to 3½ weeks. The size and progress of the 450 mμ peak (Figs. 4 and 5) allowed an assessment of the immediate state of the fetus and a prognosis to be given. Sufficient guidance was usually given by these 2 tests. However, in certain circumstances, for example where a planned intervention at 36 or 37 weeks meant induction under unfavorable obstetric

conditions, a third test was sometimes performed to establish the relative urgency of delivery.

Tests were done at once on patients seen for the first time late in the third trimester. The information from these tests together with the patient's serologic findings and past obstetric history, the state of the present pregnancy and any complications, the husband's phenotype and blood groups, and medical or postmortem reports on previous babies were collected and discussed by the hospital Rh Committee. This committee comprising obstetricians, pediatricians, and pathologists was concerned not only with planning the best time and method of delivery but also with ensuring that all parties involved in the care of mother and baby were forewarned and prepared, an advantage emphasized by Allen[1] and Vaughan.[16]

The practical policy evolved in relation to liquor analysis has been more or less that bottom zone courses (Figs. 4 and 5) imply delivery about term with surgical induction being used if the patient goes more than a few days beyond the due date. Mid-zone courses indicate premature induction graded from 38 to 35 weeks depending on their position and slope. Peaks located in or courses entering the top zone imply serious affliction and impending fetal death. The decision as to management is simple if the discovery is made after 33 or 34 weeks. Earlier than this, the problem involves philosophy as well as obstetrics, whether to temporize, with fatal results for many babies, for the sake of the odd resilient fetus who will last perhaps 3 more weeks or whether to induce labor promptly so that at best each baby is given some slight chance of survival and at worst intrauterine death with its attendant maternal risks and problems is avoided.

The type of case on which these tests and deliberations have been made and the results obtained are shown in Fig. 11. There is a clear trend toward earlier delivery with increasing severity of anemia. Naturally, in many instances the precise timing and method of intervention were influenced by other factors, for example, diabetes mellitus, hypertension, placenta previa, or previous cesarean section. Moreover, it must be reiterated that the clinical material changed considerably during the course of this investigation. The extension of amniocentesis to all patients with antibodies, irrespective of past history, has provided many more opportunities for careful judgment to influence favorably the baby's chance of survival.

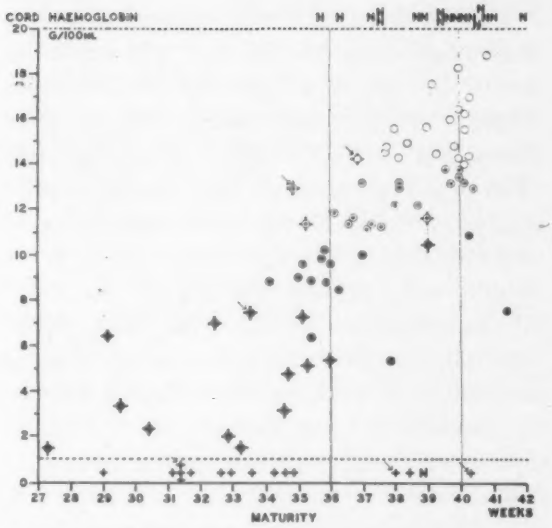


Fig. 11. Clinical results. Severity of anemia is plotted against maturity at delivery time or on intrauterine death. The convention of symbols is the same as for Fig. 4, except that circles superimposed on crosses indicate neonatal deaths. The arrows indicate deaths in which there were contributing factors. For the liveborn babies, these were (from above down) gastroenteritis, adrenal hemorrhage, and fetal exsanguination from placenta previa cesarea. For the intrauterine deaths (left to right), staphylococcal amnionitis, intrapartum asphyxia, and acute intrauterine pneumonia. These latter 3 babies were all severely affected by hemolytic disease. The stillbirth of an unaffected baby followed spontaneous accidental hemorrhage in a hypertensive woman who had diabetes. The dotted line connects a pair of monochorionic twins.

Comment

The present report confirms the claims of Bevis[6, 7] and Walker[17] that the spectral absorption curve of liquor amnii presents diagnostic features in hemolytic disease and shows that the size and progress of the characteristic peak on 450 mμ reflect the severity of anemia.

This good correlation is surprising for the absorption peak on 450 mμ appears to be caused by bilirubin,[7] yet the cord bilirubin content concentration shows only a poor correlation with the cord hemoglobin level (Fig. 8). This anomaly and the very poor correlation between the cord bilirubin level and the size of the 450 mμ peak (Fig. 9) suggest two possibilities. Either the cord bilirubin does not reflect fetal tissue levels, especially as the samples were taken from the umbilical vein, on the efferent side of the placenta, or alternatively the cord level may alter rapidly with disturbances in placental function late in labor. The latter explanation may account for the occasional very high cord bilirubin levels in association with insignificant anemia. However, the instances of low cord bilirubin levels in babies with very severe anemia are more difficult to explain especially as the liquor specimens showed the very large pigment peak consistent with this severe hemolysis. The empiricism of the correlation between the liquor peak on 450 mμ and the severity of anemia does not detract from its clinical usefulness. The test is simple, convenient, and, with a few simple precautions, reliable.

The biochemical estimation of the pigments in liquor would seem not only an unnecessary refinement[7] but also an undesirable complication for the concentrations are low, the effects of photolability and contamination by fetal serum are not avoided and may be more difficult to detect, and further variation may be introduced by dilution errors and deterioration of reagents. Equally, however, naked eye assessment or the measurement of icteric index is a dangerous oversimplification, for oxyhemoglobin in dilution imparts an icteric tinge which is of no prognostic value.

The early test and the later repeat practiced in the present series appear much more helpful than the single test pronounced sufficient by Walker,[17] for not only the size but also the trend of the 450 mμ peak provides guidance. On the other hand, the early start and repeated samplings at less than fortnightly intervals advocated by Bevis[7] seem unnecessarily vigorous.

The claim of Walker[17] that specimens must be obtained before the thirty-fifth week has not been confirmed. There is no sudden change in the gradation of severity after 34 or 35 weeks (Fig. 4) but rather a steady fall in the limits of normality throughout the third trimester. Similarly Walker's claim that specimens must be fresh does not appear correct. Sterile specimens protected from light keep admirably with or without refrigeration (Fig. 2, *A*) and this observation has led to a postal diagnostic service.

In practice, the information provided by liquor analysis frequently does little more than confirm the expectation based on the previous history[18, 19] but even here the effort is not entirely wasted. As pointed out by Walker[17] the patient who is reassured that, as anticipated, all is well gains considerable peace of mind. At the other extreme, the patient with a severely affected fetus at 28 or 30 weeks is often grateful that some effort to assess and help the baby has been made. However, even in these two groups of patients surprise findings in liquor analyses are common enough to make the procedure worthwhile. The opinion of Bevis[7] that, in considering premature induction, "in all cases of doubt clinical judgment must take precedence over laboratory results by themselves," is difficult to accept at face value. The fact that severe affliction is often so clinically silent and unexpected is the very reason why some direct method of assessment is necessary.

The discovery and salvage of the severely anemic "first-known affected" baby is most rewarding, especially for the parents, for the prospects of success in subsequent pregnancies might be very slim. In both logic and practice, the first stillbirth or neonatal death should be the easiest and the best one to avoid. The assessment from liquor is also most helpful in the primigravida sensitized by transfusion in childhood or adolescence, for in this type of patient antibody titers can mean very little and there are no previous babies to suggest a level of severity.

Another practical problem is presented by the multipara whose antenatal care in previous pregnancies has been perfunctory. Particularly if she is seen first late in the current pregnancy the discovery of antibodies neither confirms nor denies their existence in previous pregnancies. Commonly, her history includes one or more stillbirths or neonatal deaths. Usually there is a plausible reason for each of these mishaps but equally there is a dearth of postmortem reports or blood investigations. The entire history may be most suggestive of hemolytic disease, and liquor analysis can add useful substance to this suspicion.

The precise clinical action taken on the data from liquor analysis may not coincide everywhere with practice in the National Women's Hospital. The test cannot distinguish the mildly affected baby from one unaffected. From the point of view of practical obstetrics, this is no defect. However, it has led to a reluctance to use the test as a screen to determine whether a given patient can be delivered in a rural maternity annex or whether she should be confined in a base hospital. The baby with no anemia but a positive Coombs reaction presents no obstetric problem but may rapidly develop jaundice. The adequate assessment and treatment of hyperbilirubinemia may be dangerously delayed in the absence of a laboratory service.

Liquor analysis is a test for anemia which, if severe, might warrant premature delivery. In the controlled trial of unselected premature induction reported by Mollison and Walker,[13] it was found that the severity of affliction as judged by anemia was the same in liveborn infants whether or not labor had been induced. No such criticism can be leveled at the results shown in Fig. 11, which show a clear trend toward earlier induction with increasing severity of anemia. Certainly some babies with hemoglobin levels of 8 to 12 Gm. per 100 ml. at 35 to 37 weeks would still have been alive at term. But with equal certainty some would not (Fig. 4), and this risk was considered to offset the small improvement in maturity.

The readiness with which intervention is practiced in such circumstances depends on many factors, the safety and confidence with which surgical induction of labor and oxytocin drips are used, the resolution to set a limit to the induction-delivery interval, the quality of pediatric care, and the adequacy of laboratory services, particularly the availability of blood and facilities for microbilirubin estimations. But, if these services are lacking in a hospital, the rhesus sensitized patient should in all fairness be transferred to somewhere where they are available.

Hemolytic disease may provide only a small proportion of the perinatal loss in a hospital's statistics but most of these losses occur in a small number of patients. Within reason, the pre-eclamptic primigravida whose baby dies has good prospects for future successful delivery. For the diabetic or hypertensive patient, the prospects should not be lowered much. But for the rhesus sensitized patient, the outlook may be very poor. For this reason, every pregnancy of a rhesus sensitized patient should have most careful management. This report indicates that liquor analysis can provide much of the information on which such management can be based.

Summary

1. The spectrophotometric findings in liquor specimens from 101 rhesus sensitized pregnancies have been described.

2. The absorption peak on 450 mμ is larger in the presence of hemolytic anemia, but the limits of normality change with maturity.

3. The size and trend with maturity of the 450 mμ peak provide an indication of the severity of anemia and of the prognosis for the fetus.

4. The clinical application of the information from liquor analysis has been discussed.

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Fetomaternal transfusion

A case report

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FETAL bleeding into the placenta is not rare, although such bleeding into the maternal circulation has been reported uncommonly. Weiner[22] was the first to suggest the possibility but was unable to prove it conclusively. Chown[3] later reported the first authenticated instance. Since the latter's report, approximately 15 additional cases have appeared in the English literature.[1, 2, 4-7, 9, 10, 14, 18, 20] Recently, attention has been focused on this entity in pediatric treatises dealing with the pale newborn infant with hemorrhagic anemia subsequent to fetomaternal transfusion.[5, 18, 20] Much less has appeared in recent obstetric literature.[7, 19] It is the purpose of this presentation to report such a case in order to acquaint those responsible for the initial management of the newborn child with this commonly undiagnosed fetal complication.

History. K. C., a white female infant was delivered at term as a frank breech with minimal assistance on Feb. 3, 1959, at the United States Army Hospital, Fort Leonard Wood, Missouri. The primigravid mother had no history of bleeding or other complications. Immediately after the uneventful delivery, the infant appeared pale, listless, and had a weak cry and grunting respirations.

Physical examination. The infant weighed 2.7 kilograms and measured 19 inches in length. Pallor was marked, respiratory rate was 90 per minute, and apical pulse was 130 per minute. The liver was palpable but not enlarged and the spleen was not palpable. No jaundice or edema was evident.

Laboratory data. Cord blood studies revealed a hemoglobin level of 6.8 Gm. per cent, hematocrit determination 19 per cent, and total serum bilirubin level 0.2 mg. per cent, 0.1 mg. per cent indirect. Family blood group data are detailed in Table I.

Tests of the mother's serum on a panel of selected blood specimens with saline suspended cells, followed by the indirect Coombs technique, were negative for atypical antibodies.*

Fetal hemoglobin in the maternal serum was 4 per cent (normal is 2 per cent) as determined by the electrophoretic method of Singer and associates.[21]† No hemoglobin was demonstrable in the maternal urine post partum. Gross examination of the placenta revealed no evident defects.

Course. The infant was placed on oxygen and mist initially. Two transfusions of whole blood, 55 c.c. and 45 c.c., were given, the first at 3 hours of age, the second at 14 hours. The infant responded well with increasing activity, im-

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The views expressed herein are those of the authors and do not necessarily represent those of the Medical Corps, United States Army.

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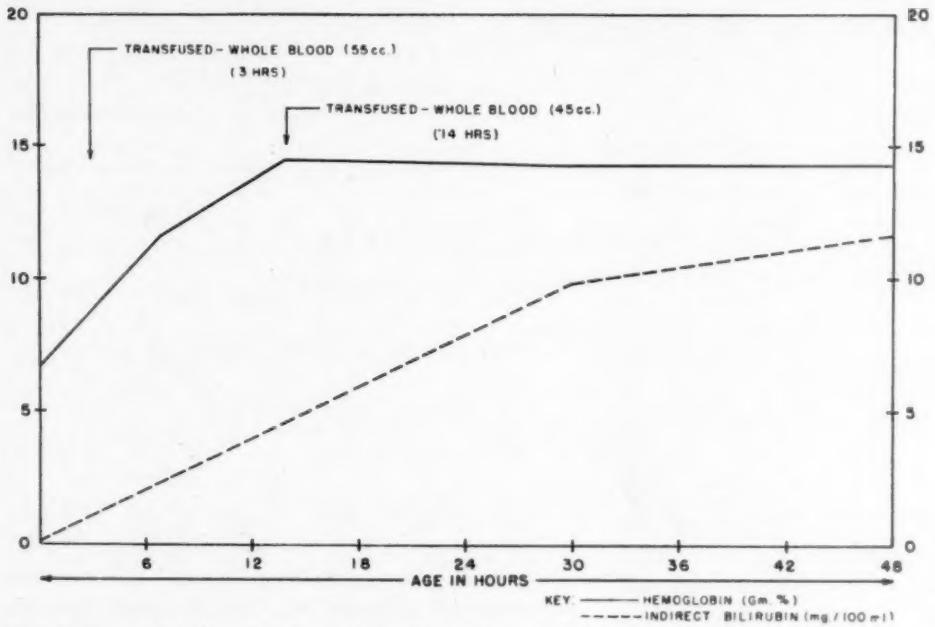


Fig. 1. Hemoglobin and indirect bilirubin values.

proved color, and cry. Peripheral venous hemoglobin response can be followed in Fig. 1.

Jaundice was first evident at 30 hours. Total serum bilirubin level at this time was 10.1 mg. per cent, indirect 9.8 mg. per cent. Total bilirubin reached a peak of 12.4 mg. per cent at 48 hours while the indirect was 11.6 mg. per cent (Fig. 1). At 48 hours of age, the infant was clinically less jaundiced and thus no further determinations were indicated or performed.

Subsequently, the infant has done well on oral iron therapy and otherwise routine management. Anemia has not recurred.

Comment

Placental defects permitting the passage of fetal formed elements have been proved by many authors, generally in conjunction with Rh isoimmunization studies.[8, 11, 15, 16] Such gross defects have been associated etiologically with several reported cases of fetomaternal transfusion.[14, 20] Microscopic defects of villous erosion permitting leakage of fetal blood into the maternal placental vascular spaces have been demonstrated by Kline.[13] Schiller[20] found fetal erythrocytes in maternal placental vascular structures. Others have been unable to demonstrate such defects in cases with elevated fetal hemoglobin, as was true in our case. Though somewhat nonspecific, the term "placental incompetence" used by Cooperman[7] seems an apt pathophysiologic description.

Spectrophotometric determination of maternal levels of fetal hemoglobin of all pale newborn infants in O'Connor's[17] series revealed 24 instances of elevated levels (above 2 per cent hemoglobin F) in approximately 8,000 deliveries. Not all such infants required transfusion therapy. Thus, the approximate incidence in his series, disregarding severity, might approximate 1 in 300 newborn infants.

Assessment of total fetal blood loss is complicated. Utilizing a method similar to that of Pearson and Diamond,[18] we estimated the loss at 145 c.c. (10 per cent [per cent total weight as blood volume] × 71 kilograms [maternal weight] × 12.3 Gm. per cent [maternal hemoglobin] × 2.0 per cent [fetal hemoglobin above normal]) or roughly two

Table I. Blood group data

	Blood group	*Rh genotype*	*Coombs*
Mother	O	CDe-cde (R_1r)	Negative
Infant	O	CDe-cde (R_1r)	Negative
Father	A	cde-cde(rr)	--

thirds of this infant's blood volume (total approximately 230 c.c.). The loss must have been slow and prolonged or greater cardiorespiratory difficulties would have been manifested with such massive loss.

The majority undoubtedly passed into the maternal circulation for there was neither excess antepartum or postpartum bleeding nor retroplacental hematoma. No funic vessel anomalies were present. No maternal difficulties occurred similar to the immediate transfusion reactions reported by Chown and Goodall.[3, 9] Maternal antibody formation was impossible because of the similarity of fetal and maternal blood groups (Table I).

The ultimate proof lies in the elevated alkali-resistant fetal hemoglobin of 4 per cent found on the second postpartum day. The upper limit of normal utilized by most authorities[18, 19, 21] is 2 per cent. Its usual uncomplicated disappearance from the maternal circulation occurred within 6 to 8 weeks post partum. This nears the fetal erythrocyte life span of 30 to 46 days postulated by Hollingsworth.[12] A follow-up determination could not be obtained.

Such elevations also appear in Cooley's anemia, myelophthisic anemia, and high altitude adaptation syndromes. In view of the absence of maternal anemia (12.3 Gm. per cent) and atypical antibody formation (Table I), none of these factors could cause this elevation.

Additional laboratory demonstration of morphologic and immunologic abnormalities caused by the transfusion, as used by other investigators,[10, 19] were not utilized because of maternal and fetal blood group similarities.

Though the above considerations are of interest, prompt diagnosis and the institution of proper therapy are of transcendent importance when one is confronted with such a pale newborn infant. Differential diagnosis includes asphyxia pallida, hemolytic anemia, and transplacental bleeding. There were no fetal or maternal complications sufficient to cause asphyxia pallida. Hematologic studies on the newborn eliminated the second possibility. The jaundice at 30 hours probably resulted from the breakdown of red blood cells, for the blood administered was nearing its expiration date. Thus, we must conclude by exclusion that we were dealing with occult fetal bleeding into the maternal circulation resulting in posthemorrhagic anemia, all without the use of complicated electrophoretic fetal hemoglobin determinations. Such procedures are time consuming and not available in all laboratories.

Once the diagnosis is established, therapy must be instituted, either whole blood or packed cells for those with large and/or more rapid loss, or iron for the moderately anemic infant whose loss was not excessive.

Maternal prognosis will be determined primarily by the presence or absence of dissimilar fetal and maternal blood groups and secondarily by the amount entering the maternal circulation. Morbidity and mortality will be that of transfusion reactions. Fetal mortality will vary with the amount and rapidity of blood loss. Prompt institution of proper therapy will generally have a salutary effect. In the case described above, blood loss was certainly significant but therapy was prompt and adequate, thus securing an excellent result. The loss could have been so rapid and massive as to cause intrauterine death without any evidence of excess maternal bleeding. Further study of the purportedly inexplicable stillbirth along the lines of placental abnormalities, maternal blood studies, and so forth might lead to a more satisfying explanation, some possibly on the basis of significant fetomaternal transfusion.

Summary

A case is presented in which fetal bleeding into the maternal circulation is thought to have occurred in an otherwise uneventful pregnancy, resulting in an anemic, distressed newborn infant.

Addendum. Samet and Bowman (Am. J. Obst. & Gynec. 81: 49, 1961) recently reported a case of fetomaternal transfusion and ABO incompatability resulting in maternal intravascular hemolysis, fibrinogenopenia, and lower nephron nephrosis.

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Severe erythroblastosis in a primigravida associated with absence of Rh chromosomes

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IN 1950 Race and associates[1] described a rare blood type having antigenic formula D--/D--. The authors interpreted such a finding as due to absence of the Rh genes (E, e, C and c).

In this communication we intend to report a case of severe erythroblastosis fetalis in the first baby of a patient of the same genetic constitution.

Case report

The mother of the propositus, A. M. S., was an 18-year-old white woman in her first pregnancy, who was being treated for pre-eclampsia. On Oct. 4, 1956, she was admitted to the Rio Piedras City Hospital because of convulsions associated with vomiting and generalized edema. The blood pressure was 160/100. The urine albumin was 4-plus; she was not in labor. The membranes were ruptured and labor began at 3 P.M. At 2:20 A.M. on Oct. 5, 1956, a 5-pound girl was delivered spontaneously in good condition but with abundant secretions in the respiratory tract. Penicillin, streptomycin, and vitamin K were given prophylactically.

After the first 24 hours of life the baby was noted to be icteric. Moro and sucking reflexes were good; the liver and spleen were not palpable. Attempts to obtain blood for exchange transfusion failed, for all samples tested were incompatible with the baby's and mother's serum. Since the indirect bilirubin level was below 13 mg. per 100 c.c., and the baby's general condition was good, it was decided to wait and try to determine the nature of the hemolytic process. In the meantime ACTH, 100 mg., was given intramuscularly every 6 hours.

On October 8 the infant's condition became much worse; she then had generalized edema and ecchymosis; the spleen and liver were palpable 1 and 2 cm. below the costal margins; there was no Moro reflex. Five mg. of vitamin K and 50 mg. of vitamin C were administered.

An exchange transfusion was performed with the red blood cells of the mother resuspended in compatible plasma. However, the infant was in poor condition and died toward the end of the procedure.

The mother became pregnant again in 1957. Arrangements were made with the Canadian Red Cross for obtaining blood type D--/D-- for possible exchange transfusion of the baby when she delivered a macerated stillborn fetus at 7 months. At the time there were no symptoms or signs of eclampsia; the urine albumin was negative.

In July 12, 1958, a curettage was performed for incomplete early abortion (after 2 months' amenorrhea), five days before the patient had a fall.

Laboratory data. On Oct. 6, 1956 a direct Coombs test on the baby was 4-plus. Serum bilirubin level was: 1 minute (direct), 23.8 mg. per

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100 c.c.; 30 minute (total), 36.6 mg. per 100 c.c.; indirect, 12.8 mg. per 100 c.c. The hemoglobin level was 15.2 Gm.; red blood count, 4.15 million; color index, 1.1; leukocyte count, 15,800. Differential analysis showed: myelocytes, 5 per cent; juvenile forms, 6 per cent; stab cells, 22 per cent; segmented forms, 39 per cent; basophils, 1 per cent; lymphocytes, 27 per cent. There were 1,366 nucleated red blood cells per 100 white blood cells. The urine was bile positive; the blood culture was negative.

On Oct. 8 the serum bilirubin level was: 1 minute (direct), 29.3 mg. per 100 c.c.; 30 minutes (total), 41.6 mg. per 100 c.c.; indirect, 22.3 mg. per 100 c.c. The hemoglobin level was 10.8 Gm.; red blood count, 3.03 million; color index, 1.1.

Blood grouping tests gave the following results: baby, Group A, DCe/D--; mother, Group A, D--/D--, kk, Fy^a- Le^a+, SsM, P+, JK^a+; father, Group A, Dce/dce, kk, Fy^a+, Le^a+, SsM, P+, JK^a+.

Saline suspensions of the mother's red blood cells were agglutinated by anti-D (incomplete) serum. The mother's serum contained antibodies active against all red blood cells tested; the original panel of cells included Rh negative, Duffy negative, Kell negative, and P negative as well as various rh-Hr and MNS types. Further studies revealed that the only compatible blood was that having the same antigenic pattern as the patient's.

Titers of antibody against a pool of Rh positive cells were: saline agglutinins 16, plasma albumin 64, trypsinized cells 512, indirect Coombs 2,056. The baby had a direct Coombs test of 4-plus. The baby's serum agglutinated a complete panel of cells including most of the rare antigens; the only compatible bloods found were that of the mother and other bloods D--/D--. No autoagglutinins were present. Free antibodies were demonstrable in the baby's blood utilizing enzyme-treated cells (trypsin) and the indirect Coombs technique; saline agglutinins were negative. The indirect Coombs titer was 64.

Comment

Very few persons have been reported with the rare Rh type D--/D--. They include the original case of Race and co-workers.[1, 2] The peculiar genotype is attributed by Race and his group as being the product of absence of that part of the chromosome containing the genes E, e, C and c. They also concluded that this type of defect is in favor of the idea that the order of the genes is DCE.

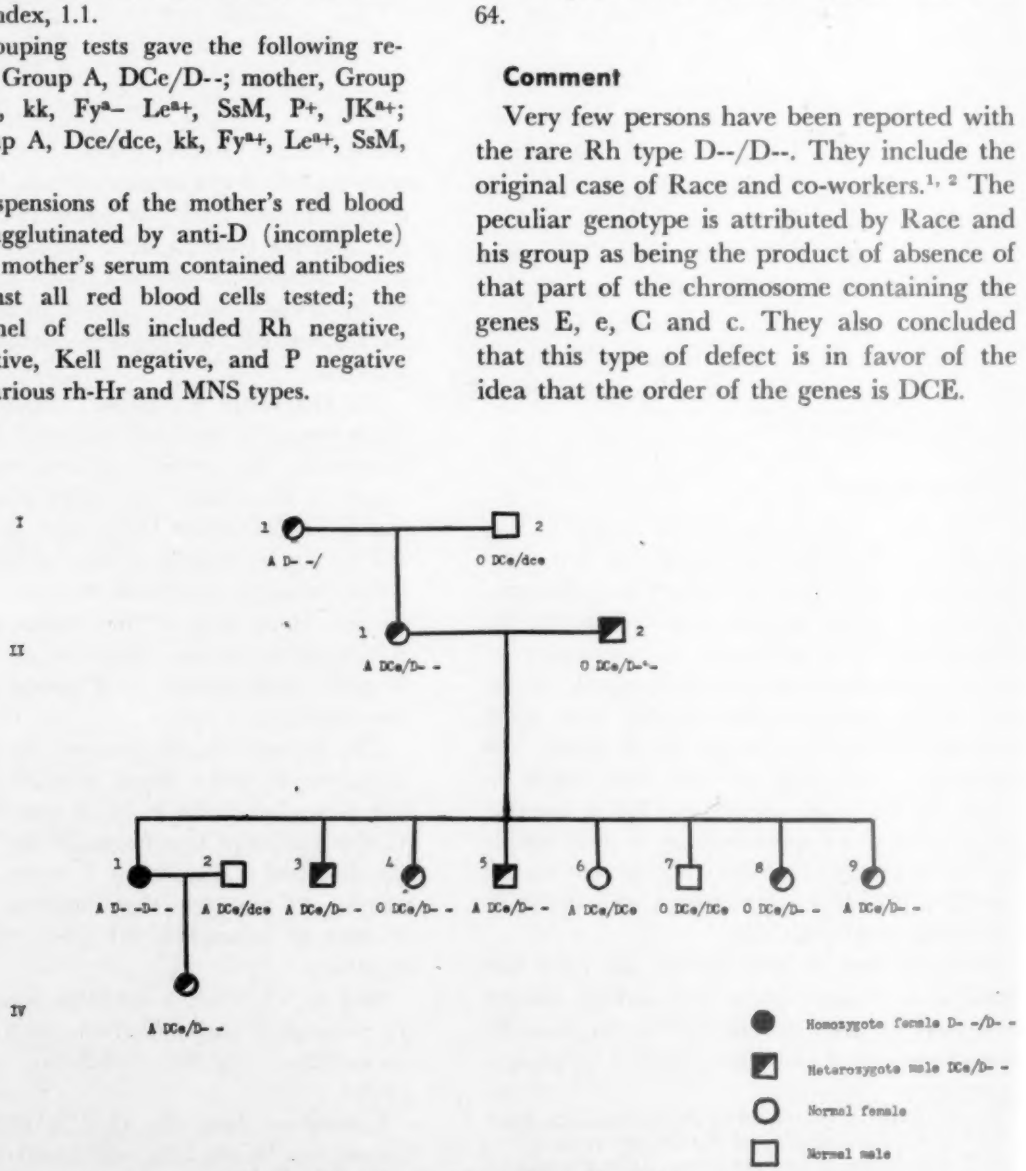


Fig. 1. Geneology. (Propositus: III, 1.)

A group of patients (7 homozygous and 14 heterozygous) was reported by Buchanan[3, 4] among members of the Canadian Indian tribe Mitis. Two examples of Rh defect were also studied by Waller and Sanger[5] among an American family. McLawhorn[6] refers to a case of erythroblastosis in the baby of a patient with absence of factors C, c, E, and e. Levine,[7] in a study of sera submitted to Ortho Research Laboratory for identification of atypical antibodies, found one resulting from a D--/D-- patient.

An important determinative factor in all the cases mentioned has been consanguinity. Most of the cases have been unveiled when difficulty has been encountered in cross-matching for blood transfusion or when erythroblastosis developed in the baby of an Rh-positive mother.

Absence of E and e allelomorphs has been reported by Wiener.[8] Wiener interprets the above-mentioned genotype as well as the one described by Race, Sanger, and Selwyn[1] as being due to new genes RH^{ou} and Rh^{ox} and not to absence of Rh chromosomes. Henningsen[9] has recently reported a partially defective chromosome involving (d--) or a triple deletion (---) of Hr factors cde.

The case studied by us presents certain interesting features:

1. No history of consanguinity could be elicited, but this is always difficult to exclude. Our patient represents the first reported case occurring without intermarriages.

2. Severe erythroblastosis was the outcome of the first pregnancy of an 18-year-old mother having no previous history of parenteral therapy with blood or blood products. McLawhorn[6] also observed early neonatal death of the firstborn of a young mother with an Rh defect, but the patient had received blood transfusions several years before; the results of the autopsy on the baby were inconclusive. The second baby died in utero at 5 months; the third baby had erythroblastosis with hydrops and died a few hours after birth.

3. The value for conjugated (1 minute, direct) bilirubin glucuronide was very high, this being a very rare finding in the early stages of erythroblastosis. The mother's history of eclampsia and the finding of areas of focal necrosis in the infant's liver at postmortem examination may have some bearing on this point.

The laboratory studies in our case revealed certain facts which we believe are worth discussing. At first there was considerable difficulty in determining the true Rh type of the mother, as some of the anti-C and anti-E reagents were not pure and a positive reaction was obtained due to the presence of incomplete anti-D. It has been shown that patients with the antigenic formula D--/D-- will give a positive agglutination when their red blood cells are suspended in saline and only anti-D serum containing incomplete antibodies is added.[2] By means of pure anti-C, anti-E, and anti-c reagents it was shown that the blood under consideration lacked C, E, c, and e because tests with the available anti-e also gave a negative reaction.

The strong antibodies found in the mother's serum included a mixture of weak complete antibodies (saline agglutinins, titer 1:16) and incomplete antibodies with an indirect Coombs titer of 1:2,056. Although specific absorptions have not been done, it is theoretically possible that the serum may contain antibodies against all the missing Rh factors. As the baby's blood was DCe/D-- the antibodies which are most probably present are anti-c and anti-E. It is also theoretically possible that the patient may have anti-d.

In constructing a family tree (Fig. 1) several known factors were utilized. All members of the family except the mother and the father of the propositus' generation III *(1, 2)* gave positive reactions with anti-D, anti-C, and anti-e and negative reaction with anti-c and anti-E. The genetic constitution could be interpreted as either DCe/DCe or DCe/D--. The dosage effect was utilized which tends to differentiate homozygotes. Scoring with anti-D sera gave no noticeable differences. When testing with anti-C a stronger reaction was obtained with bloods from generation III *(6* and *7)* and they were interpreted as being homozygotes DCe/

DCe; the other members of the family as heterozygotes and belonging to the type DCe/D--. No homozygote D--/D-- was found among the siblings of A. M. S. (generation III, *1*). The husband of the propositus (generation III, *2*) gave positive reactions with four anti-Rh sera and was classified as DCe/dce.

An important point to remember with regard to treatment is that in cases of erythroblastosis fetalis the blood of the mother is always compatible and exchange transfusion can be performed with the mother's packed red blood cells provided she is in adequate physical condition for blood donation. Unfortunately, in our case the bloods of the baby and mother were not studied by one of us (M. V. T.) until the day before death and when exchange transfusion with the mother's red blood cells was performed it was too late to be of any use.

Summary and conclusions

1. A case of severe erythroblastosis in the firstborn of a young woman having the rare antigenic pattern D--/D-- has been presented; the mother had no history of injection of blood or blood products.

2. No history of consanguinity was elicited in the family of the propositus.

3. The literature related to cases of Rh defects has been reviewed.

We are deeply grateful to Dr. Philip Levine, Ortho Research Laboratory, Raritan, New Jersey, for his valuable cooperation. Valuable assistance obtained from the personnel of the Blood Bank, School of Medicine, San Juan, Puerto Rico.

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The erythroblastosis problem

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THE obstetrician is frequently in a quandary when dealing with the sensitized Rh-negative pregnant patient.[1, 2, 12] Early induction of labor may result in a premature unaffected child who dies because of its immaturity. Allowing the pregnancy to proceed to full term may result in a stillbirth, fetal death in utero, or severe affectation of the infant. How much credence one can place in antibody titers is often a matter of dispute. Why some sensitized mothers will continue to be delivered of little or nonaffected babies, while others will have intermittent or continuous fetal damage, is as yet unanswered. Each new case raises new problems.

Objectives

The problem initiating this study was whether intrapartum or postpartum maternal sensitization in the Rh-negative woman was common and, if so, to what degree it was a factor in producing erythroblastosis in the offspring. We also attempted to discover whether maternal or paternal genotypes, both in the Rh and international blood types, in any way affected the fetal outcome. A corollary of the study was to discover to what degree of accuracy the maternal Rh antibody titers could be relied upon to predict the fetal prognosis. We also sought to determine whether the fetal antibodies conformed to the maternal titer. Finally, we sought to determine whether there was a factor common to all sensitized infants which could be used, ante partum, to select those who would be severely affected.

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Methods and materials

All Rh-negative mothers, private and staff, were included in this study which was conducted from Dec. 15, 1957, to June 30, 1960. A total of 115 patients were surveyed, of whom 47 had sufficient data and follow-up studies to be included in this investigation. Of these, 23 mothers were Rh sensitized and 24 nonsensitized, although 3 of the latter had infants with ABO incompatibility. All patients included in this study had maternal and fetal Rh typing, genotyping, and international typing done. Whenever the father was known, paternal genotype, Rh type, and international type were investigated. During pregnancy, both saline and albumin antibody titers were obtained in the first, second, and early third trimesters, and weekly from the thirty-sixth week to term. This was continued post partum, weekly, to the sixth week and monthly thereafter as long as possible. Each newborn infant's blood was subjected to the Coombs test, Rh and international typing, genotype, hemoglobin, bilirubin, and free Rh antibody titer tests. Whenever clinically warranted, anti-A and anti-B titers were done. No selection of patients was made other than on the completeness of their hospital data and follow-up tests.

Results

Maternal blood groups. Reference to Table I will show that the only essential difference in international blood types in mothers whose infants were sensitized as opposed to those who were not was that there

Table I. Maternal international blood groups

	A	*AB*	*B*	*O*
Rh-negative sensitized mothers	7	3	3	10
Rh-negative nonsensitized mothers	10	0	4	10

were 3 mothers with type AB in the sensitized group, whereas there were none in the nonsensitized group. Furthermore, 2 of these 3 mothers were delivered of stillborn erythroblastotic babies, and the third was delivered of an infant requiring 3 exchange transfusions. Eighteen infants of 13 mothers sensitized to the Rh factor required exchange or supplemental transfusions and, since 3 were from AB mothers they represent 16.6 per cent of the severely affected infants. There were only 3 fetal deaths of infants of sensitized mothers and 2 of these mothers were of the AB international type. These 3 AB mothers represent 13 per cent of the 23 mothers sensitized, over twice the incidence of AB adults in the general population. The Rh antibody titer levels and parity in these mothers did not vary significantly from the Rh-sensitized mothers of the A, O, or B international types. While we realize that this is a small number on which to draw definite conclusions, these data suggest that Rh-negative sensitized mothers of international group AB will be delivered of more severely affected babies than similarly sensitized mothers of other blood groups.

In considering maternal Rh genotypes, an interesting fact came to light. Two mothers had C and one had E in their genotype. None of the infants of these mothers were stillborn or required exchange or supplemental transfusion. By contrast, 13 of the remaining 20 mothers had infants requiring transfusion. In the nonsensitized group, there was only 1 patient who had E in the genotype. Although the numbers are again small, it is suggested that once sensitization to Rh antigen occurs in the mother, C or E may be a protective influence against severe fetal affection. The lack of greater numbers of C or E in the Rh genotypes of nonsensitized mothers makes it clear that these antigens do not prevent Rh sensitization per se, but may block or ameliorate fetal sensitization in infants subject to D antibody.

Paternal blood groups. Consideration of the distribution of the international grouping of fathers of the infants in this study shows no significant difference among those siring affected or unaffected babies. Nor was there any particular group evident in fathers producing severely affected infants as opposed to those producing slightly affected ones. There were 1 B and 2 O who fathered the infants that died, and 7 O, 2 A, and 1 B who fathered those infants requiring exchange or supplemental transfusion.

Turning to the paternal genotypes, our data show, that of the husbands of the 23 sensitized mothers, 17 were heterozygos and 6 homozygos for D. Of the 13 of this number whose offspring required supplemental transfusion or exchange transfusion, 6 husbands were homozygous and 7 were heterozygous for this D factor. All of the 10 husbands of sensitized mothers whose infants required no treatment after birth were heterozygous for the D factor. Only 11 genotypes of husbands of Rh-negative mothers, who showed no Rh antibody titer, were available. Of these, 6 were homozygous and 5 heterozygous for D. These data are consistent with the greater possibility of production of an affected infant if the father is homozygous rather than heterozygous. The genotypes of the 23 husbands of Rh-negative sensitized mothers and genotypes of 11 husbands of Rh-negative nonsensitized mothers are illustrated in Table II. Seven paternal Rh genotypes occurred. Comparison of the genotypes of fathers of severely affected infants with those requiring no treatment showed 4 homozygous CD in the former group and none in the latter group. Other than that, there was no predominant genotype in the 23 fathers of the sensitized group or 11 fathers of the nonsensitized group. This material suggests that an infant carrying a CD genotype inherited from the father has a greater chance of developing erythroblastosis than one inheriting the D factor alone.

Fetal blood groups. Blood groups in the offspring of D sensitized and nonsensitized mothers were compared. When the 45 infants of 23 sensitized mothers were divided into those requiring transfusion and those requiring no therapy, no significant differences were noted in their blood groups (Table III). Likewise, no striking distribution was apparent when this group was compared with the offspring of nonsensitized mothers. The genotypes of the infants of sensitized and nonsensitized mothers showed no difference and no single genotype predominated in the more severely affected infants.

Maternal Rh antibody titer. Both saline and albumin antibody titers were done on the study patients as previously described. A titer elevation or drop was considered present when a change greater than a one-tube dilution from the previous titer in either antibody was evidenced. Table IV illustrates our findings. Of 23 infants of the sensitized mothers, whose titer levels were available all through pregnancy, 4 with increasing titers had affected infants and 5 with increasing titers had nonaffected infants. One of those with increasing titers was delivered of a nonaffected infant who was Rh negative. As can also be seen in Table IV, equal numbers of sensitized mothers with titers, which remained relatively stable, had affected and nonaffected infants. No mother bearing an erythroblastotic baby had a titer drop, whereas one sensitized mother with a titer drop gave birth to an Rh-negative baby. These statistics were a most interesting result of our study. They illustrate what many of us have long suspected. With a titer rise in a sensitized mother, one could correctly predict the production of an affected infant only 50 per cent of the time. If the titer remained stable, we would expect this group to be delivered of unaffected offspring, yet our data indicate that the fetus will be affected in half of the cases. Since this is exactly the conclusion one could arrive at by flipping a coin, the prognostic significance of the antibody titer is thus somewhat attenuated. While the obstetrician may suspect, with a titer rise, an affected baby, he will

Table II. Paternal Rh genotypes

Genotype	*Husbands of sensitized mothers*		*Husbands of nonsensitized mothers (unaffected infants)**
	Of infants requiring transfusion	*Of infants not requiring transfusion*	
CDe/CDe	2	0	2
CDe/Cde	3*	5	2
cDe/cde	4†	4	1
CDe/CDE	2	0	0
cDe/CDe	1	1	0
cDE/CDe	1	0	4
CDE/cde	0	0	2

*Unaffected infants—those requiring neither exchange nor supplemental transfusion.

†Denotes dead infant.

Table III. Fetal international blood groups

	A	*AB*	*B*	*O*
Offspring of Rh-negative sensitized mothers (45)				
Requiring transfusion	5	3	2	8
Not requiring transfusion	9	3	2	13
Offspring of Rh-negative nonsensitized mothers (22)	6	1	5	10

Table IV. Maternal Rh-antibody titer change

Affected infant			*Nonaffected infant*		
↑*Titer*	↔*titer*	↓*titer*	↑*Titer*	↔*titer*	↓*titer*
4	7	0	5 (1 Rh neg.)	6 (1 Rh neg.)	1 (1 Rh neg.)

Table V. Maternal antibody titer

Titer	*Affected infants*	*Nonaffected infants*
1:4	0	1
1:8	1	0
1:16	0	2
1:32	4*	0
1:64	0	1
1:128	1 D*	1
1:256	4 D†	4
1:512	1	0
1:640	0	1
1:1024	2 D†	0

*Severely affected infant.

†Infant died.

be correct only half of the time and premature induction of labor or cesarean section for a suspected erythroblastotic infant may result in a premature infant who dies because of its prematurity, but is otherwise unaffected. Likewise, failure of maternal titer to rise should not lull the clinician into a false sense of security, since half of these mothers will likewise be delivered of affected babies. The conspicuous conclusion of these data is that a much more reliable test, prognostically, than maternal Rh-antibody titer must be found if we are to predict fetal affection and avoid intervention which will result in premature unaffected infants.

The question of whether admixture of maternal and fetal blood at delivery produces maternal sensitization to the Rh antibody concerned us. Abruptio placentae, cesarean section, and manual removal of the placenta are these conditions which will produce this admixture to the greatest extent. In order to test this hypothesis, purposeful manual removal of the placenta was performed on a number of sensitized and nonsensitized mothers. In the sensitized group, there were 5 cesarean sections with manual removal of the placenta. In 3 of these, there were no significant titer changes post partum. In one, there was a titer rise at 4 weeks post partum and in another a titer drop at 4 weeks postpartum. In the nonsensitized group, there were 5 cesarean sections with manual removal of the placenta, and no antibody titer developed post partum in any of these. Six additional patients in this group had manual placental removal following vaginal delivery and in none of these was a postpartum titer evident. Only in one patient did a titer develop de novo post partum. Two additional sensitized patients had a postpartum titer rise without manipulation and 4 additional women in this category had a postpartum titer drop. There was one abruptio placentae in the sensitized group of mothers, and this patient showed a titer drop post partum. One must conclude, therefore, that although postpartum Rh sensitization may occur, it is rare, and cesarean section, abruptio placentae, and manual placental extraction do not seem to significantly enhance maternal antibody formation.

One further question must concern us before we leave the subject of maternal antibody titer. Does the maternal titer level, prior to delivery, have any prognostic significance on fetal outcome? Our experience in this matter is recorded in Table V. Titers of mothers of infants who were sufficiently severely affected to require either exchange or a supplemental transfusion ranged from 1 : 8 to 1 : 1024. While the maternal titers in the nonaffected infants never reached the level of 1 : 1024, the lower titers did not indicate the severity of the fetal disease. The infant, whose mother's titer was 1 : 8, required 3 exchange transfusions. One infant, whose maternal antibody level was 1 : 32, was severely affected. A maternal antibody titer of 1 : 128 resulted in a severely affected infant who died. The only baby with hydrops fetalis in this series had a mother whose titer was only 1 : 256. In sensitized mothers who were delivered of infants requiring no treatment, the levels ranged from 1 : 4 to 1 : 640. There were exactly the same number of infants in the affected and nonaffected group at a maternal titer level of 1 : 256. These data suggest, therefore, that at term maternal levels above 1 : 1,000 indicate a poor prognosis for the fetus, but below this level the maternal titer is a poor criterion for fetal affection.

Fetal sensitization. The Coombs test has been long used as an index of fetal sensitization. Such reliance has been placed on this test that, on it alone, many clinicians base their decision for exchange transfusion in the newborn of a Rh-incompatible marriage. It interested us to determine whether such trust was justifiable. Of the 13 affected babies of sensitized mothers requiring exchange or additional transfusions, there were one 2-plus, one 3-plus, and eleven 4-plus Coombs tests. Of those infants requiring neither exchange nor supplement, there was one each of 1-plus, 2-plus, and 3-plus, and seven 4-plus Coombs tests. Thus, the Coombs test should be interpreted to show only the

presence of maternal antibody on the fetal red cell or in the fetal serum, but it is not a reliable indicator of the need for treatment of the infant.

Since the Coombs test is not a reliable guide for transfusion of the newborn, what other tests might we use? The circulating antibody titer of the fetus might be useful in some cases, so we began to investigate its feasibility. Table VI gives our results. It can be seen from this table that both the affected and non-affected babies ran the gamut from no titer to a titer of 1 : 128. Of the nonaffected infants, one Rh-negative baby had a titer of 1 : 8 and one a titer of 1 : 64. There was no consistency between the maternal and fetal titers. However, it should be noted that 7 of the 13 affected infants and 5 of the 6 most severely affected infants, including all 3 of those who died, had circulating antibody levels of 1 : 1 or below; whereas only one of the nonaffected infants reached this level. This might suggest that, in the more severely affected infant, the antibody is fixed on the fetal red cell leaving a low circulating titer. Taken together with other data, a low circulating fetal antibody level would indicate severe fetal affection.

The most reliable tests, in our hands, for determining the necessity for fetal exchange transfusion have been the fetal hemoglobin and bilirubin. A hemoglobin level of less than 14.0 Gm. per cent should make the clinician suspicious of the need for exchange transfusion, and below 12.0 Gm. per cent, immediate exchange transfusion should be done. The hemoglobin level during the usual 3 to 5 day stay in the newborn nursery cannot be dismissed as final, for some infants in this series required supplemental transfusion 3 to 5 weeks after delivery because of a slowly developing anemia, although their hemoglobin at discharge was within normal limits. The most severely affected infants in our study had the lowest hemoglobin level, which conforms to the experience of others. Bilirubin elevation is usually a later manifestation of erythroblastosis rather than anemia. Bilirubin levels in the newborn above 5 mg. per cent should excite suspicion of a need for exchange, whereas levels of 10 mg. per cent or higher, in our experience, require immediate exchange transfusion.

Table VI. Fetal circulation antibody at delivery

Titer	*Affected infants*	*Nonaffected infants*
0	4*	1
Trace	2 DD†	0
1:1	1 D*†	0
1:4	0	1
1:8	1	2 (1 Rh negative)
1:16	1	0
1:32	2*	1
1:64	0	1 (Rh negative)
1:128	2	3
1:256	0	1

*Severely affected infant.
†D Infant died.

Table VII. Pregnancy where maternal sensitization first occurs

	Pregnancy						
	1	*2*	*3*	*4*	*5*	*6*	*7*
No.	1*	13	2	1	0	1	0

*Given injection of blood as child.

Maternal sensitization. In Table VII, the reader can see the pregnancy in which maternal sensitization first occurred. Information in this regard was available in only 18 of the 23 sensitized mothers. The patient who developed sensitization in her first pregnancy was given an injection of her parents' blood in childhood and was delivered of an infant that required exchange plus supplemental transfusion. A great majority of mothers in our study were sensitized in their second pregnancy. This coincides with other investigators' findings that it requires at least one previous pregnancy to sensitize an Rh-negative mother with an Rh-positive husband. It can also be seen that sensitization occurred for the first time as late as the sixth pregnancy. Of the 24 nonsensitized mothers, 5 had achieved a parity of 4 or greater without sensitization occurring. It is possible, therefore, to have multiple pregnancies without sensitization, but if such sensitization does occur, it would be most likely to do so in

the second pregnancy. What effect does an affected baby have on the prognosis for future normal infants? The first child of the patient who had been sensitized by her parents' blood in childhood required exchange transfusion, but in 3 successive pregnancies no treatment was required. One study patient had a stillborn child in her third pregnancy but was delivered of 2 infants, subsequently, both of whom required exchange transfusions, however, they survived. Another patient was delivered of 2 successive stillborn infants and one who died in the neonatal period. Thus, the delivery of an erythroblastotic infant, even stillborn, does not of necessity condemn all succeeding pregnancies to doom. The likelihood of succeeding pregnancies producing affected babies certainly increases following the delivery of a sensitized infant, but the severity of the erythroblastosis bears no constant relationship with that baby and succeeding siblings.

ABO incompatibility. Three patients in the nonsensitized Rh-negative group had 4 pregnancies and were delivered of 5 infants who had ABO incompatibility. All of the mothers were of the international blood Group O and, of the fathers, 2 were B and one was A. No Rh-antibody titer was ever evident in either the mothers or the infants. Since each of these 3 cases presents a slightly different problem, they will be presented separately below.

Case 1. The mother's blood group was O with a C in her Rh genotype. The father was B, Rh positive (cDe/cde). The infant that was delivered was B, Rh negative. The maternal titers taken on the first postpartum day showed an anti-A titer of 1:16 and an anti-B titer of 1:4. The fetal bilirubin was 15 mg. per cent at birth, but rose to 29 mg. per cent and the infant became severely jaundiced. It required 2 exchange transfusions for the bilirubin to return to normal levels. The Coombs test was negative.

Case 2. This patient had 2 pregnancies while under observation and had known previous ABO sensitization. Her husband was A, Rh positive (CDe/cDE). The maternal anti-A titers were 1:16 at 36 to 38 weeks, 1:128 at delivery, and 1:32 2 days post partum. The anti-B titers were 1:256 at 36 weeks, 1:64 at 38 weeks, and 1:16 postpartum. The newborn was Group A, Rh positive (CDe/cde), who had a bilirubin of 9 mg. per cent which never rose, and the infant never became jaundiced or required treatment. During the next pregnancy, with the same husband, the patient exhibited anti-A titers of 1:2 at 30 weeks, 1:16 at 34 weeks, 1:4 at 37 weeks, and 1:12 at delivery. The anti-B titers were 1:4, 1:64, 1:16, and 1:32 for the same periods. The newborn was O, Rh positive, with a bilirubin of 2.7 mg. per cent. The Coombs test was negative and the infant was not given an exchange transfusion.

Case 3. This patient had a B, Rh-positive husband and was delivered of twins. Since this was the first pregnancy exhibiting BO incompatibility in this patient, no antibody titers were done during the pregnancy. Twin A had a bilirubin which rose to 21 mg. per cent and required an exchange and 2 supplemental transfusions. Twin B had a bilirubin which reached 19 mg. per cent and required one exchange transfusion. The maternal titers one day post partum were: anti-A 1:4 and anti-B 1:8. Both twins were B Rh positive and their Coombs tests were negative.

Several observations can be made about these 3 cases. First, it is apparent that all of these ABO incompatible infants were born of nonsensitized Rh-negative mothers. This confirms the general impression that, in the face of ABO incompatibility, the Rh sensitization either does not occur or affects the infant to a minor degree. Second, one may conclude from the case histories that the maternal anti-A or B titer level is no more accurate or reliable an index for fetal therapy than the maternal Rh titer. The 2 mothers, of the 3 infants that had exchange transfusions, had anti-A titers of 1:16 and anti-B titers of 1:8, whereas the mother, of 2 infants not requiring transfusion, had anti-A titers of 1:128 and 1:2 in her 2 pregnancies. The fetal bilirubin level appears to be the most reliable laboratory test on which to base the need for treatment of the ABO incompatible infant. Finally, it can be observed that the Coombs tests were negative in all of these infants, which is again consistent with the general experience elsewhere.

Comment

Although the original objective of this study, to find maternal sensitization as a result of delivery, was not realized, some rather worthwhile byproducts of the investigation resulted. Since we have heretofore based our decision for premature induction of labor or cesarean section to remove an incompatible fetus from a sensitized maternal environment on rising maternal titers,[10, 15] the data here presented suggest that, using these criteria, we would be correct in only 50 per cent of the cases. In half of the cases, therefore, one would chance the delivery of a premature but otherwise unaffected baby, which, in our opinion, is too great a calculated risk in obstetric practice. In like manner, of those mothers in whom there is no titer rise, 50 per cent will be delivered of affected infants, lulling us into a sense of false security. Furthermore, the absolute level of maternal titer in this study bore no constant relationship to the degree of fetal disease. All of this points to a more accurate and predictable test in the mother for the determination of which infants will show stigmas of erythroblastosis and which will not. Since thus far we have been unable to prevent maternal sensitization or block Rh antibody formation with any great success, it makes such a test more imperative in Rh-sensitized mothers if we are going to achieve increased fetal salvage in this group. We have developed a test which may meet this need and which we will report on in the future, after its worth can be sufficiently substantiated.

One additional fruit of this investigation was the finding of AB, Rh-negative mothers in the sensitized group and their absence in the nonsensitized group. They represented over twice the normal population incidence of the AB blood group and accounted for most of the cases of severe infant disease. While the number of cases is admittedly small, it does suggest that the total maternal blood genotype[3] (international plus Rh), rather than the Rh alone, may affect the production of maternal antibodies to a greater or lesser degree, and so allow us to predict more accurately which patients will be delivered of erythroblastotic infants. In the same vein, 3 out of 23 sensitized mothers who had C^7 or E in their Rh genotype were delivered of unaffected infants, while the remainder had neither of these factors and had affected children. This suggests to us that the determination of Rh negativity in the mother is insufficient and the entire Rh genotype should be determined. Again, since the numbers of cases are small, we cannot come to any definite conclusions, but the data suggest that the total Rh genotype of the mother may also be a factor in determining whether she will produce anti-Rh antibodies of a type deadly to her infant. Considering the paternal Rh genotype, this study suggests that CD genotype may be potentially more sensitizing to the mother and thus indirectly more deadly to the infant than D is alone. All of these data would seem to indicate that complete international and Rh studies should be done on Rh incompatible marriages to the extent of determining which combinations of all these factors present potential danger to the fetus.

The Coombs test, in our experience, by itself, does not serve to indicate the need for fetal therapy. The presence of a low fetal circulating Rh-antibody titer (1 : 1 or below), at birth, accounted for half of the erythroblastotic infants and for all of the severely affected ones. This test, then, may, with further experience, prove a valuable guide in the determination of a need for exchange transfusion. Fetal hemoglobin and bilirubin, at present, still remain our most reliable indices for this need.

While our study indicated that the delivery of an erythroblastotic baby will usually be followed by affected infants in successive pregnancies,[9, 11, 13] it failed to explain why a mother can intermittently be delivered of affected and unaffected babies in spite of constant or rising sensitization. Since the capacity of the sensitized mother to produce antibodies is enhanced by successive pregnancies, all other things being equal, one would expect that her offspring would be progressively severely affected. We have

demonstrated that this is not always so, and, since it is not, we must explain this inconsistency by some other means. It seems to us, considering our data, that a reasonable explanation is that the placental permeability or integrity varies with each pregnancy. If the placenta is more permeable to fetal cells or permeable in both directions, more antibody would thus be presented to the fetus and greater and longer red cell destruction would occur. Because the integrity of the placenta varies from pregnancy to pregnancy in the same mother, this could account for the inconsistency of appearance of fetal erythroblastosis in successive pregnancies in the sensitized woman. All that remains is to devise a test for placental permeability.

The ABO Rh-incompatible pregnancies,[4, 5, 6, 8, 14] in this study, confirm the general impression that the Rh incompatibility is of lesser significance than the ABO problem when they occur in the same patient. Our data also confirm the general observation that the Coombs test is not helpful in determining ABO sensitization in the newborn. However, we have also demonstrated that the ABO-incompatible infant may be in as tenuous a condition as the Rh-incompatible one, since 3 of the 5 infants in this group had marked bilirubin elevation and required exchange transfusions. ABO incompatibility is probably more common than the Rh type and can be equally as dangerous to the infant. Finally, our data support the idea that maternal anti-A and anti-B titers are no more valuable in indicating fetal prognosis than maternal anti-Rh titers.

It is hoped that the reader can help to confirm or deny the observations herein presented. Since the management of the pregnancy of an Rh-negative sensitized mother is still an unsettled and difficult matter, and since no single individual or group has the opportunity for wide experience in this problem, we would welcome further investigation, or the experience of others, into the questions which have been raised in this article.

Summary

1. Forty-seven cases of Rh incompatible pregnancies at the University of Miami School of Medicine, Jackson Memorial Hospital obstetric unit have been presented. Twenty-three of these occurred in sensitized mothers and 24 occurred in nonsensitized mothers.

2. The presence of the AB international blood group in the Rh-negative mother appears to be an important factor in the production of severely affected infants.

3. C or E in the maternal Rh genotype may be a protective factor to the infant of a sensitized mother.

4. CD in the paternal genotype is probably a greater sensitizing factor to the mother than D alone.

5. The maternal Rh antibody titers only correctly predict fetal affection in half of the cases indicating a need for a more sensitive and more reliable test in order to prevent delivery of premature unaffected infants.

6. The maternal titer levels of 1 : 1,000 or over indicate an affected infant. Below this level, no constant relationship exists between the titer and the fetal outcome.

7. The absence of circulating Rh antibodies or the low titer of these antibodies in the newborn of a sensitized mother appear to indicate a poor fetal prognosis.

8. The inconstant affection of successive pregnancies in Rh-sensitized mothers suggests the theory that the determining factor may be the variable degree of placental permeability in each gestation.

9. Infants of ABO-incompatible unions may be as severely affected and require as immediate therapy as Rh-incompatible infants.

10. Maternal anti-A and -B titers are a poor index of fetal prognosis in ABO incompatibility.

11. Intrapartum or postpartum maternal Rh sensitization occurs, but rarely, and cesarean section, abruptio placentae, and manual placental extraction cannot be implicated in such sensitization when it occurs.

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Neuroblastoma as a cause of antenatal death

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MALIGNANCIES of the sympathetic nervous system are not rare.[1] However, these lesions infrequently have their start in the antenatal period and seldom progress far enough to cause intrauterine death. This case is of interest because extensive involvement of visceral organs by neuroblastoma tissue presumably led to antenatal death of a full-term fetus in whom Rh incompatibility was suspected.

Case report

Maternal history. Mrs. A., a 25-year-old white primipara, had a normal prenatal course except for mild water retention which was controlled by a low-salt diet. Her blood type is B III, Rh negative, and that of her husband is O IV, Rh positive. She gave no history of previous transfusions and had no antibodies when tested during each trimester of pregnancy.

During the thirty-ninth week of gestation, fetal heart tones and fetal movements, which were recorded regularly during previous visits, disappeared. Intrauterine death due to unknown causes was diagnosed.

At approximately 40 weeks' gestation the patient went into natural labor and was delivered of a term-sized macerated fetus by low-forceps extraction. The fetus had a somewhat edematous appearance and a distended abdomen. These findings, together with a large placenta, suggested to the clinicians that the fetus might be hydropic because of erythroblastosis.

Gross postmortem examination.

External surface. The body was that of a white male infant weighing 3,925 grams and having a crown-heel length of 51 cm. and crown-rump length of 35 cm. The body was moderately macerated with large areas of skin missing from the body surface. The face was slightly edematous and the abdomen markedly distended but there were no visible malformations.

Head. The head was normal in proportion to the rest of the body. The bones of the calvarium seemed of normal thickness and appearance. The brain was severely macerated and in a semiliquid state. The orbital and nasal cavities and the base of the brain were normal. The membranes of the brain showed no evidence of lesions.

Neck. The organs and structures of the neck were normal.

Thorax. The pleural and pericardial cavities contained small amounts of dark brown liquid. The organs and structures of the thoracic cavity appeared normal except for the lungs which were not expanded. No gross evidence of neoplastic growth could be seen.

Abdomen. The peritoneal cavity contained a small amount of dark brown liquid as a result of maceration. The intestinal tract was normal throughout its length. The liver was uniformly enlarged and weighed 390 grams. The surface was smooth and glistening. The consistency of the liver seemed to be firmer than usual. On the cut surface its color was light brown. No evidence of tumor infiltration or congestion was apparent. The spleen was of normal size and weighed 15 grams. Periaortic sympathetic ganglia and retroperitoneal lymph nodes were not enlarged.

Genitourinary system. The left adrenal gland appeared to be replaced by a firm, round, well-encapsulated tumor which depressed the upper pole of the left kidney. Both the tumor and the left kidney were surrounded by perirenal fascia and fat. The tumor measured 5 cm. in diameter and weighed 43 grams. The cut surface was reddish brown. The tumor was solid. No hemorrhage or cystic areas could be seen. Adrenal cortical tissue could not be identified. The right adrenal weighed 5 grams and appeared normal.

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Kidneys, ureters, and the bladder appeared normal, although the left kidney weighed slightly less than the right.

Skeletal system. All the bones appeared normal and there was no evidence of bone metastasis.

Placenta. The placenta weighed 1,240 grams and measured 22 by 21 cm. The cotyledons were well demarcated, thick, and of soft consistency. Small hematomas were noticed on the cut surface. The maternal surface had a reddish yellow coloration.

Microscopy examination.

Liver. Only a small amount of liver tissue was still visible and most of the parenchyma was replaced by islands of tumor cells (Fig. 1). The islands were fairly uniform in size and appeared to be separated by sinusoidal tissue which in a few places had parenchymal cells persisting. The extent of maceration obscured the exact relationship of the tumor cells to the finer structures of the liver.

Left adrenal. The central portion contained innumerable islands of large uniform cells with prominent hyperchromatic nuclei. These were identical to those found in the liver and are characteristic of the pattern generally designated to neuroblastomas. No rosette formation could be seen. The masses of tumor tissue appeared to be largely within sinusoids and extended peripherally toward the definitive cortex but did not seem to invade this area (Fig. 2).

Right adrenal. This gland retained its normal histologic appearance. However, a few small islands of typical tumor cells were contained in the sinusoids of the medulla.

Lung. The tissue was moderately macerated but histologic details could still be made out fairly well. The alveoli were not expanded. Small groups of tumor cells were scattered throughout the parenchyma. The majority appeared to be in the lymphatics surrounding medium-sized veins but interstitial tissue unrelated to large blood vessels also contained scattered groups of tumor cells. Neoplastic cells could be seen in areas of the visceral pleura immediately adjacent to the pulmonary tissue.

Spleen. The general appearance was normal except for mild degenerative changes secondary to intrauterine death. Tumor cells could be identified in the peripheral part of the wall of the large vein and in several irregular spaces which were probably lymphatic channels.

Kidneys. Changes secondary to intrauterine

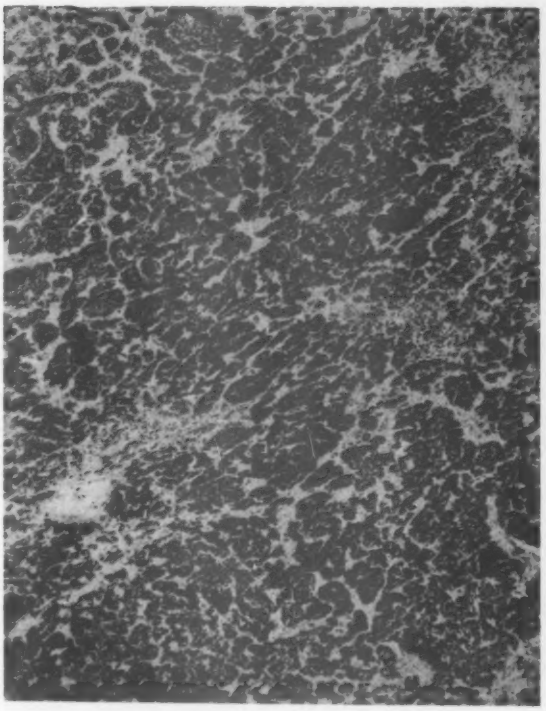


Fig. 1. Low-power view of the liver showing uniform replacement of liver parenchyma by tumor islands. The tumor is undifferentiated with no evidence of rosette formation.

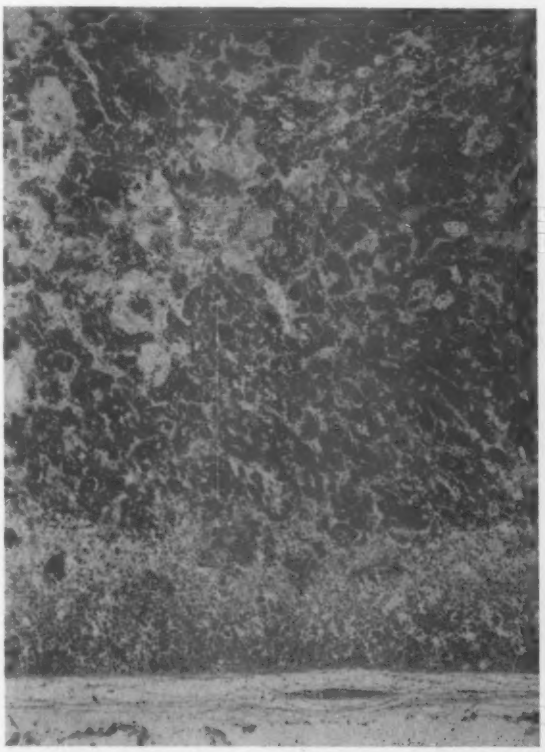


Fig. 2. Low-power view of the left adrenal showing masses of tumor tissue within the sinusoids. The definitive cortex is free from invasion.

death made differentiation of tumor cells somewhat difficult and for the most part it was impossible to be certain whether groups of cells were actually neoplastic or whether they were undifferentiated nephrogenic tissue. Only in one area could a large mass of tumor cells positively be identified, in the interstitial tissue a short distance beneath the capsule. Other areas were highly suggestive of tumor formation. In addition, parts of the connective tissue surrounding the kidney was infiltrated by tumor cells.

Placenta. The villi were unusually large. The blood vessels seemed somewhat reduced in number and there was an unusual amount of connective tissue containing many histiocytes of the variety generally designated as Hofbauer cells. In some places scattered Langhans cells were still visible beneath the syncytial covering of the villi. In many places the surface was separated suggesting that there had been considerable edema.

No sections of the brain, skin, skeletal system, thyroid, thymus, or other visceral organs were taken because of the advanced stage of maceration of the fetus.

Comment

The neuroblastoma is one of the most common and most highly malignant tumors of infancy and childhood. Approximately half of the reported cases are in infants less than 2 years old and 75 per cent in children less than 4 years old.[2] The occurrence of neuroblastoma in the fetus and newborn is relatively uncommon. In an extensive review of the literature, Wells,[3] in 1940, was able to find only 17 authenticated cases. Bachmann,[4] in 1955, reported 650 cases of neuroblastoma which included 3 cases in stillborn, 31 in the newborn, and 51 in the first 3 months of life. Gross,[5] in 1959, reported on 217 cases at the Boston Children's Hospital, his youngest patient being 4 hours old and his oldest 16 years. Within recent years the occurrence of tumors in adolescent and even adult patients has been clearly recognized.

The neuroblastoma may develop in any site where sympathetic ganglion cells or their precursors are located. Their growth takes origin from undifferentiated neural tissue of sympathetic ganglia or the adrenal medulla. In fact, 3 types of tumors may derive from this tissue—the pheochromocytoma, the ganglioneuroma, and the neuroblastoma. The latter is the highly malignant form of sympathetic ganglion tumor, and is made up of only poorly differentiated anaplastic imitations of neuroblasts which are, of course, the precursors of adult ganglion cells. The neuroblastoma, therefore, is truly an embryonic tumor since it arises from immature tissue which never attains completely adult differentiation.

Microscopically neuroblastomas are diffuse masses of rounded cells resembling large lymphocytes with frequent mitosis which might explain why neuroblastomas originally were considered round cell sarcomas.[6] Even today we find a wide variety of descriptive terminology in the literature for the same tumor (neurocytoma, sympathoma embryonale, sympathicoblastoma, sympathogonioma). The wide range of differentiation of neuroblastomas undoubtedly accounts for these specific terms.

In the least differentiated tumors round celled growth is dominant and rosette formation is often indistinct or absent. The first recognizable stage of neuron differentiation is the appearance of rosettelike clusters of cells. Further differentiation converts some of the pyroform neuroblasts into recognizable young nerve cells and their outgrowing axons into bundles of parallel fibers which will stain specifically as nerve fibers.

About 40 per cent of neuroblastomas originate in the adrenal medulla. Other sites are the sympathetic chains of the abdomen, neck, and thorax—in that order of frequency. Probably none originate in the central nervous system.[2] Metastatic spread may be via either the lymphatic system or the blood stream and secondary lesions may appear rapidly in a variety of locations. The bones, especially the calvarium and orbit, and the liver are the most frequent sites of metastasis. In cases of neuroblastoma in the newborn the enlargement of the liver is most striking. Hagstrom[7] reports on a case in which a 700 gram liver caused dystocia in a newborn infant. Richards[8] records a liver

weighing 1,850 grams in a 2-week-old infant. Occasionally, rupture of a blood vessel in the liver, eroded by neoplastic tissue, has caused hemoperitoneum and dystocia. Early metastasis of neuroblastoma to the bones is not as common in the newborn as in the age group between 2 and 4 years. Metastasis to the lungs and other visceral organs is rare at any age.

This case is of interest not only because of a neuroblastoma causing antenatal death but also because of the occult involvement of multiple organs by tumor tissue. Except for the well-circumscribed, encapsulated left adrenal neoplasm, no gross evidence of tumor metastasis was detectable. The commonly described discrete, rounded, white, or hemorrhagic metastatic nodules were completely lacking. The tumor cells apparently were uniformly scattered and a well-integrated part of the organ involved. This raises the old question again as to whether we are dealing with a multicentric proliferation of undifferentiated sympathetic cell groups in these organs or with metastatic lesions. The wide distribution of sympathetic cells in the body certainly could give support to this theory. The lack of tumor cells in the placenta in our case would seem to speak against a blood-borne metastasis from the adrenal tumor. At least a number of cases in the literature, especially those in which no primary tumor site was apparent, also support the theory of multicentric origin of neuroblastomas. Potter and Parrish[9] reported a case of a stillborn fetus in which all tissue of nervous origin, except the brain, had undergone neoplastic hyperplasia. Recently Gross[5] reported 4 instances of multiple neuroblastomas apparent at necropsy. Of these, one child was found to have 6 separate tumors arising from different parts of the retroperitoneal sympathetic chains, all presumably having arisen independently. Multiplicity of these lesions must clearly depend on influences affecting many parts of the developing tissues simultaneously and we may well be dealing with a systemic disorder of the sympathetic nervous tissue as a whole.[10]

Summary

A mature stillborn fetus is described in which a small, well-encapsulated neuroblastoma of the left adrenal gland was the only gross finding. Microscopic examination revealed diffuse neoplastic involvement of the liver, adrenals, spleen, kidneys, and lungs. Multicentric proliferation of undifferentiated sympathetic cell groups in these organs is suggested.

I am indebted to Dr. Edith Potter for aid and advice.

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Intrafunicular ulceration of persistent omphalomesenteric duct with intra-amniotic hemorrhage and fetal death

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UMBILICAL vessels may rupture by trauma, usually in cases of velamentous insertion of the cord or at the level of a varicosity.[1] The rupture may lead to a complete tear of the cord or to the formation of a funicular hematoma. The former may be followed by exsanguinating hemorrhage and the latter may impair fetal circulation by compression of all umbilical vessels.[3]

Rupture of an umbilical vessel during labor with fatal hemorrhage is rare. Rupture of a vessel ante partum with fetal death is exceptional.[4] This unusual diagnosis was made in the case to be presented, but pathologic investigation revealed a still more intriguing cause for bleeding.

Case history

The mother, a gravida iv, para iii, Negro woman, was 32 years old. Her 3 children were normal. The pregnancy was uneventful until the thirty-sixth or thirty-seventh week, when labor started. The parturient did not feel fetal movements for about 24 hours before the beginning of labor. She was admitted at the onset of the first stage. The abdomen appeared abnormally enlarged and when the membranes ruptured, 2 hours and 20 minutes later, an excessive—but not measured—amount of fluid was noted. This fluid was different from the fluid observed in cases of simple maceration. It was thicker than usual and was reddish but did not contain large blood clots. A macerated stillborn male infant was spontaneously delivered after a total labor of 14 hours and 20 minutes. A tear of the umbilical cord was present close to the umbilicus.

Autopsy. The body was that of a moderately macerated and well-developed male infant weighing 3,340 grams and measuring about 53 cm. in length. A thin omphalomesenteric duct extended from an area in the ileum 26 cm. proximal to the ileocecal valve into the umbilicus. The umbilical cord stump was a pale reddish brown color. It measured 14 cm. and had the same diameter of 2 cm. throughout its length. Its cut end showed 3 vessels. About 1 cm. from the umbilicus there was a rounded mass 1.5 by 1.2 by 1 cm., located at the inferior aspect of the cord, with a smooth surface and a cystic consistency.

The upper surface of the cord showed a tear 2 cm. in length and 0.4 cm. in width extending from a point located 1.5 cm. from the umbilicus. The cord was examined by means of a series of cross sections. At the level of the umbilicus, the 3 vessels were normally placed and the omphalomesenteric duct was located in the center of the cord. Its brownish content showed on microscopic examination meconium and some red blood cells. Distally, at the level of the cystic mass, the section revealed 2 dilated structures. The smaller of these was the omphalomesenteric duct. The cystic mass itself did not communicate with adjacent structures (Fig. 1). It contained a small amount of brownish, thin fluid and its lining was smooth. More distally was the dilated

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blind end of the omphalomesenteric duct. At its superior aspect, the duct communicated widely with the tear in the cord surface (Fig. 2). The lining of the duct appeared finely folded in the other sections, but it was rather smooth at this level and coated with some meconium and black flakes of blood. The umbilical arteries ran inferior to the duct and the vein was in a still more inferior position in the cord in the proximal section and was lateral to the duct in the distal section. Examination of the placenta revealed no vascular rupture. Its amniotic surface was brownish, as was that of the cord. The weight of the placenta was 435 grams and its cut surface was not unusual. The total length of the cord was 44 cm.

Microscopic examination of multiple sections of the fetal end of the cord was made. The lining of the duct was made up largely of a gastric type of mucosa with numerous parietal cells (Fig. 3). The mucosa showed spotty cellular infiltration and large zones of eosinophilic necrosis with massive ulceration. The process had extended toward the surface of the cord and had also dissected along the vessels into Wharton's jelly. The edges of the superficial rupture were thinned out and ragged. They showed no definite traces of acute inflammatory exudate, nor did any other area in all sections. However, there were multiple small calcified granules and rounded histiocytes close to the rupture (Fig. 4), along with some well-preserved nonhemolyzed red blood cells. The cleft produced by the ulcer within the cord could be followed along the vessel wall and throughout all sections. The cleft contained small amounts of vernix meconium and some old hemolyzed

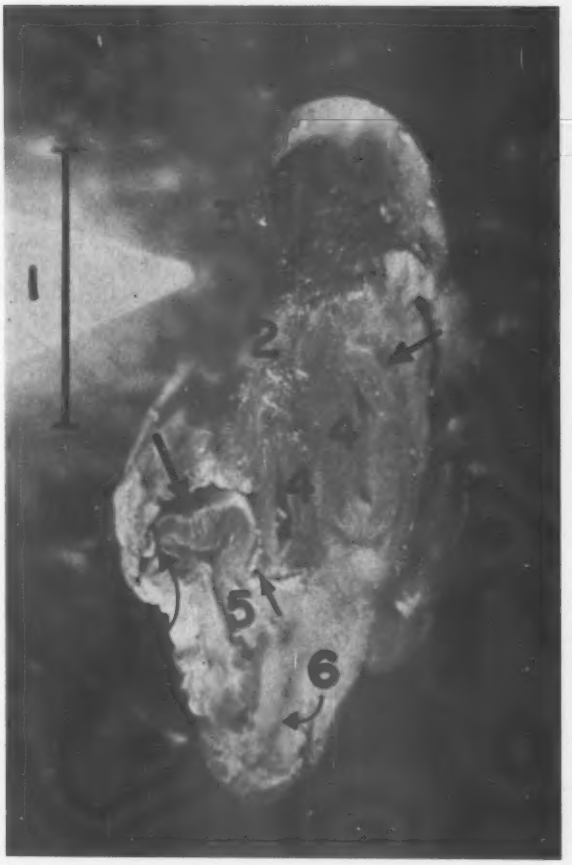


Fig. 2. Cross-section of cord showing the extent of the ulceration *(1)*. *2*, Bottom of ulceration made up of gaping omphalomesenteric duct; *3*, fresh blood clot; *4*, arteries; *5*, vein. Arrows point at artificial clefts filled with blood, cellular debris, and meconium; arrow marked *6* indicates deepest area containing debris, and arrow marked *7* is at the level of a possible venous rupture. (Original magnification approximately ×4.)



Fig. 1. Cross-section of cord proximal to the ruptured area. *1*, vein; *2*, arteries; *3*, pseudocyst; *4*, omphalomesenteric duct with blood-filled lumen. Arrows point to an artificial cleft due to intrafunicular ulceration. (Original magnification approximately ×7.)

blood, as well as nuclear debris. Along the tract, there were numerous rounded cells, probably histiocytes, resembling mobilized mesenchymal cells of Wharton's jelly. Some cells contained meconium granules, but no hemosiderin-laden phagocytes could be demonstrated. There were clumps of fresh red blood cells in many areas, chiefly in the most peripheral parts of the cord. Clumps of squames appeared embedded in the Wharton's jelly.

The cyst described grossly had no epithelial lining and its wall was covered with debris and fetal intestinal content. The meconium-filled tract in Wharton's jelly came close to this pseudocyst,[5] but no actual communication was found on section. All the umbilical vessels were completely empty. There were foci of digestion of the thinned-out vascular walls of both arteries and vein in areas abutting on the ulcer tract. In one area, the venous wall was thin and eosinophilic and it showed an area of discontinuity. On histologic grounds only and in the presence of maceration, the parts played in the apparent rupture of this vein by autolysis, digestion, and artefact could not be ascertained.

In sections of the lungs, the alveoli were diffusely expanded with hemolyzed red blood cells and contained some clumps of vernix. It was apparent that there had been a prenatal intra-amniotic hemorrhage and that the fetus was alive at this time.

Final anatomical diagnosis. Stillbirth; maceration; patent omphalomesenteric duct extending into umbilical cord; ulceration and hemorrhage from omphalomesenteric duct into umbilical cord; ulceration of umbilical cord; (?)rupture of umbilical vein; acute intra-amniotic hemorrhage; massive aspiration of bloody amniotic fluid; pseudocyst of Wharton's jelly.

Comment

The findings in this stillborn infant and the absence of known maternal or placental causes of intrauterine death suggest that death was due to the lesions observed in the umbilical cord. Death was not due to compression of the vessels by the distended omphalomesenteric duct and did not occur before the cord ruptured since the fetus aspirated bloody amniotic fluid. The absence of any clinical symptoms and the finding of concentrated blood in the lungs and the absence of hemosiderin deposit in the placenta suggest a sudden, massive and rather recent intra-amniotic hemorrhage. Known causes of umbilical cord hemorrhage

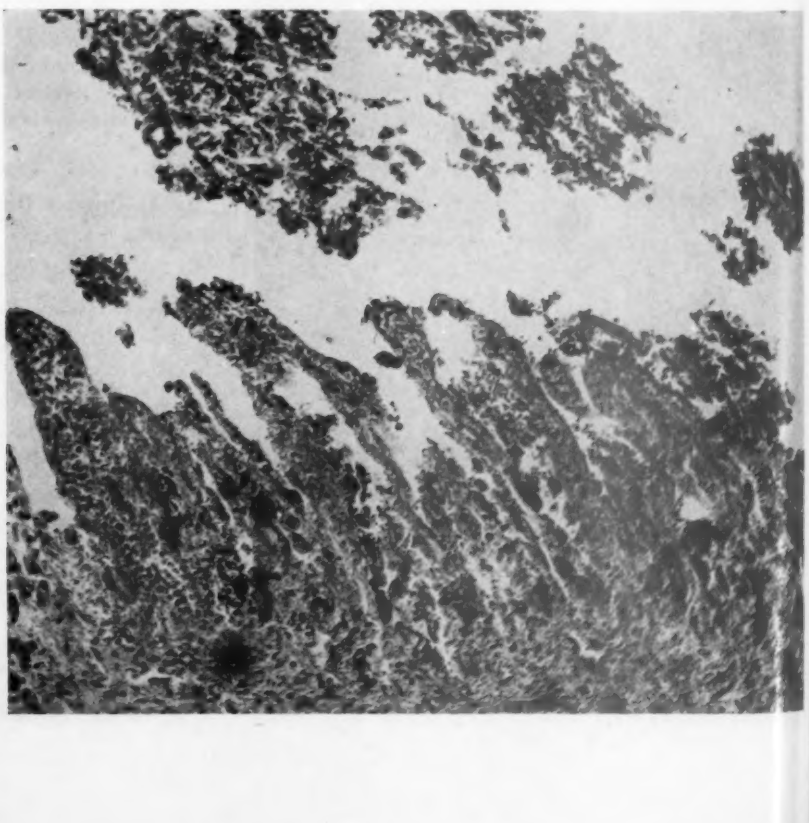


Fig. 3. Gastric mucosa in omphalomesenteric duct. The lumen contains blood and cellular debris. (Hematoxylin and eosin. ×270; reduced ⅓.)

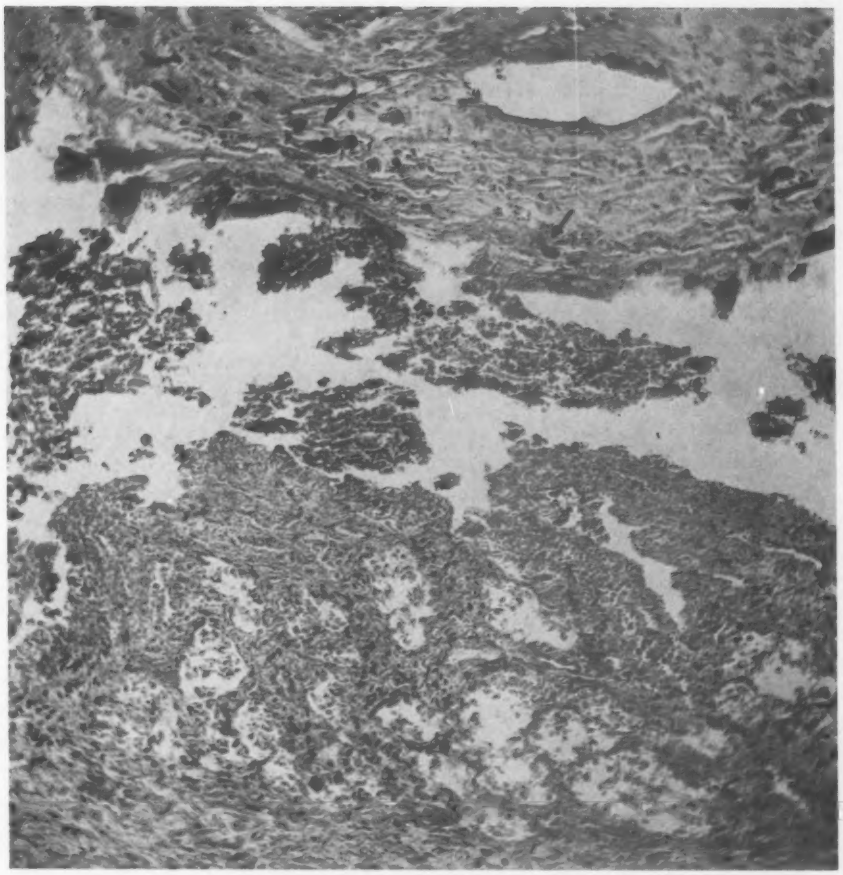


Fig. 4. Cross-section of omphalomesenteric duct at the level of the rupture. The lower wall is lined with duodenal mucosa showing superficial hemorrhage and ulceration. The upper wall mucosa has disappeared, and the underlying tissue contains calcified masses (arrows) and a few round cells. (Hematoxylin and eosin. ×180; reduced ⅓.)

include, besides vasa previa, ruptured umbilical hematoma, rupture of a varix of the umbilical vein, rupture of an artery, and complete rupture of the cord. None of these was grossly evident and none would explain the ulceration of the omphalomesenteric duct. Thus, the most probable explanation is that an ulcer of the vitelline duct developed in the vicinity of an area of gastric mucosa. As the ulcer progressively gained access to the surface of the cord, it also extended in depth within the cord. As a result, the cord was infiltrated with intestinal contents and showed a histiocytic reaction as well as focal calcification. The process probably did not extent over more than a few days since no hemosiderin was found. A final massive hemorrhage might have come either from the vitelline duct mucosa itself or from an eroded vessel, probably the umbilical vein. It seems that more intrafunicular hemorrhage would have taken place if the mucosa had bled severely prior to the ulceration and rupture of the cord surface. The severity of the hemorrhage is not a factor in differential diagnosis since Meckel's diverticulum hemorrhages may be massive.[2]

A review of the literature did not disclose a comparable case, and prenatal complications of omphalomesenteric duct anomalies are not mentioned in recent articles[2, 6, 8, 9] nor in papers describing cord hematoma[3] or vascular rupture.[4, 7] Similarly, the cause of bleeding in Jenkin's case quoted in Browne's classic article is not described further than "ulceration" of cord.

Summary

A unique case of fatal antenatal hemorrhage from the umbilical cord is reported in which the primary factor is thought to be an ulcer of a persistent omphalomesenteric duct.

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Intrafetal gas in utero

Pathognomonic sign of intrauterine fetal death

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GAS visualized roentgenographically within the fetal vascular system is recognized as pathognomonic of intrauterine fetal death. Since Roberts'[16] first description of gas within the fetal circulation, in 1944, most reports stress this finding. There are also several cases[4, 9, 14, 16] that demonstrate intraperitoneal gas or, at least, extravascular, in addition to intravascular. The case to be reported radiographically demonstrates intraperitoneal gas with no evidence of intravascular gas. The importance of this case is the demonstration that gas within the fetus is a sign of intrauterine fetal death.

Case report

B. C., a 21-year-old Negro woman, gravida iv, para iii, was referred to us for radiographic abdominal study on May 14, 1959. She had had 3 previous uncomplicated pregnancies and deliveries in 1956, 1957, and 1958, but the present pregnancy was accompanied by slight headaches, edema, and diplopia. Her weight had increased from 117 to 143 pounds. Polyhydramnios was present and fetal heart tones were not satisfactorily heard because of the increased weight and polyhydramnios. The expected date of delivery was June 22.

Roentgenograms (Figs. 1-3) revealed maternal hydramnios. There was a splayed out attitude of the fetus and an air bubble apparently within the fetal abdominal contour indicated intrauterine fetal death.

The patient was scheduled for hospital admission on May 18 for a medical induction of labor. She went into spontaneous labor on May 17 and was admitted at 7 A.M. It was then learned that the fetal heartbeat was heard clearly 2 weeks previously, but that no fetal movements were felt by the mother following this visit to the doctor. A stillborn macerated fetus was delivered at 3:25 P.M.

X-ray films (Figs. 4-7) of the stillborn fetus, taken in many positions, confirmed the prenatal radiographic finding of intraperitoneal gas. Gas in vascular structures, probably the thoracic aorta, was noted, which had not been visualized



Fig. 1. Anteroposterior supine view of maternal abdomen. Localized air density in the region of fetal abdomen.

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Fig. 2. Anteroposterior erect view of maternal abdomen. Air fluid level within fetal contour.



Fig. 3. Lateral erect view of maternal abdomen. Confirms the presence of air fluid level in fetal abdomen rather than a maternal gas shadow. No evidence of gas in fetal vasculature. Impression: intrauterine fetal death.

on the original prenatal maternal abdominal studies.

Postmortem examination. The body was that of a macerated, stillborn, male infant weighing 5 pounds, 4 ounces and measuring 43 cm. in crown-heel length. There was extreme blistering of the skin. The abdomen appeared moderately distended and no fluid wave was elicited.

The body was opened in the usual way of Y-shaped incision under water. Upon careful penetration of the peritoneum, several bubbles of gas were expressed from the peritoneal cavity. Estimated volume of the gas was 10 ml. Exploration of the abdomen disclosed faulty rotation of the mesentery in the small intestine. The mesentery appeared foreshortened, with an excess of bowel present at the periphery. At first, this gave the impression of a volvulus. However, on following the bowel from the duodenum to the sigmoid, it was found that there was a compression of the loops of bowel upon themselves and, in 2 areas, there was a small accumulation of mucoid, bile-stained material within these distended loops. The fetus was again placed under water and, when the heart was opened, several small bubbles of gas were expressed from within the heart. By milking the aorta, a few more bubbles of gas came through the incision in the heart. Upon removal of the heart, the portion that had been opened was found to be a large right ventricle. There was a vestigial left ventricle, with a large foramen ovale, which passed into a common atrium. There was coarctation of the aorta. The ductus was widely patent.

The final pathologic diagnoses were: (1) Faulty development of the mesentery in the small intestine, with incomplete obstruction at 2 points; (2) Congenital heart disease, apparent cor triloculare; (3) Coarctation of the aorta; (4) Intrauterine death; cause undetermined; (5) Free intraperitoneal, intravascular, and intracardiac gas.

Comment

Tager,[21] in 1952, presented "A New Roentgen Sign of Fetal Death," or collapse of the fetal spine in an erect film. He outlined 9 roentgenologic criteria of fetal death, including gas in the fetal circulatory system. He showed that all of these were fallible, but did not show that gas in the circulatory system was unreliable. Hence, of 10 diagnostic criteria, gas within the fetus has

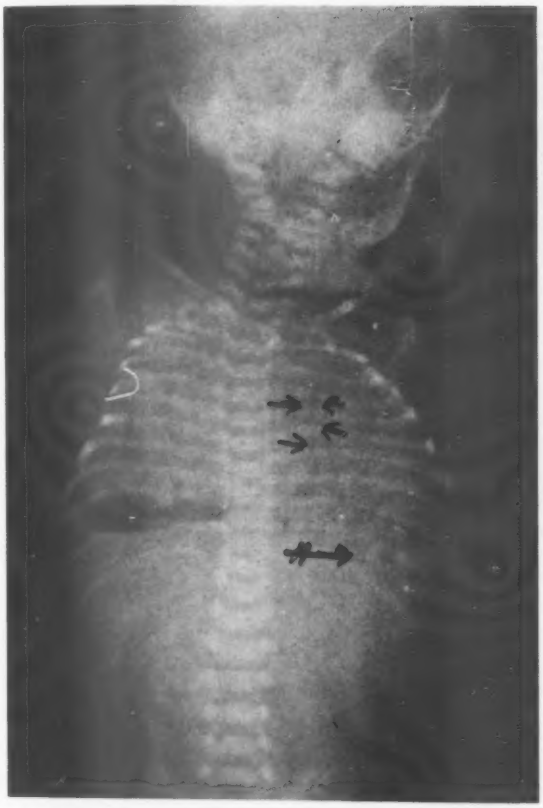


Fig. 4. Erect anteroposterior view of stillborn fetus. Note right subdiaphragmatic air and (→) air in aorta.

been the one to stand the test of time in being pathognomonic of intrauterine fetal death.

Ross,[17] in 1958, reviewed the subject and, including his cases, found that 56 cases[5-8, 10-13, 15, 18, 22] had been reported. Single cases by Weinberg and Werner,[22] Abbas and Airth,[1] and Christiansen,[3] as well as 5 cases by Stewart,[19] were not included. Subsequently, Stewart and Hytten[20] reported 6 cases diagnosed prenatally and 3 cases postnatally. One prenatal and 5 postnatal cases were reported by Bennett.[2] These, with the present case reported, bring the total recorded cases to 80. It is expected that as intrauterine gas is more frequently recognized, the number of proved cases will mount rapidly.

However, in series of cases where this diagnostic sign was known, Holm[9] found 12 out of 22 cases positive and Crick and Sims[4] found 12 out of 30 cases positive, which indicates the gas within the fetus is only present in slightly less than 50 per cent of cases of intrauterine fetal death.

Six cases,[4, 9, 14, 16] of those reported, demonstrated gas, in sites other than in the vascular system, in addition to the vascular gas. Margolis and Jones[14] and Roberts[16] each report a case showing gas both in the vascular system and in the retroperitoneal area. Crick and Sims[4] and Holm[9] each report 2 cases of gas in the vasculature and in the peritoneal space. The present case is the only one that demonstrates intra-abdominal air on the prenatal films with no evidence of air in the vascular system. Gas may be present more frequently within a dead fetus than previously noted but, if borne in mind and differentiated from maternal gas, the diagnosis may be made more frequently. Ross[17] states that the intravascular gas is seen more frequently in the lateral view than in the anteroposterior view of the abdomen and, if fetal death is suspected, a



Fig. 5. Lateral decubitus view of fetus. Note gas streak in region of thoracic aorta (→) as well as intra-abdominal gas.

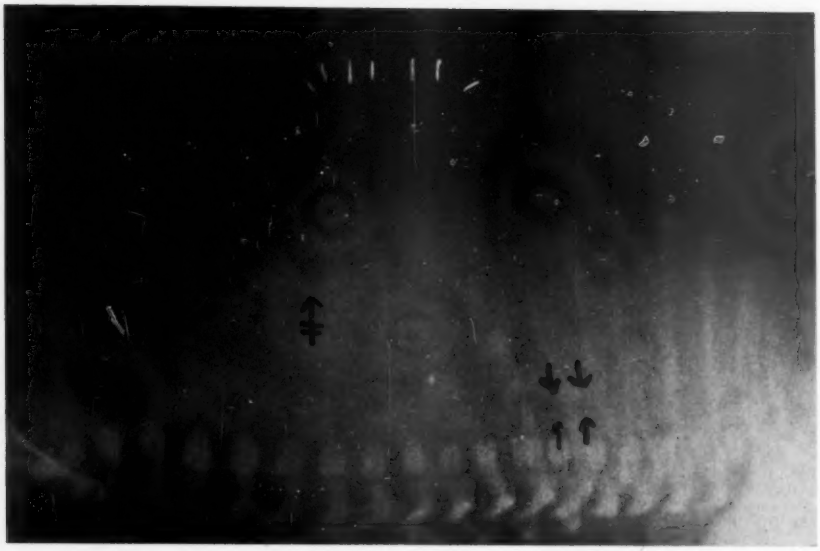


Fig. 6. Lateral transabdominal view of fetus. Note gas streak in region of thoracic aorta (→) as well as air fluid level below anterior abdominal wall.

lateral view as well as the anteroposterior view is imperative. Hence, evaluation of the lateral view for intravascular gas and intra-abdominal fetal gas in all views should increase the number of diagnoses well above its present level of 50 per cent.

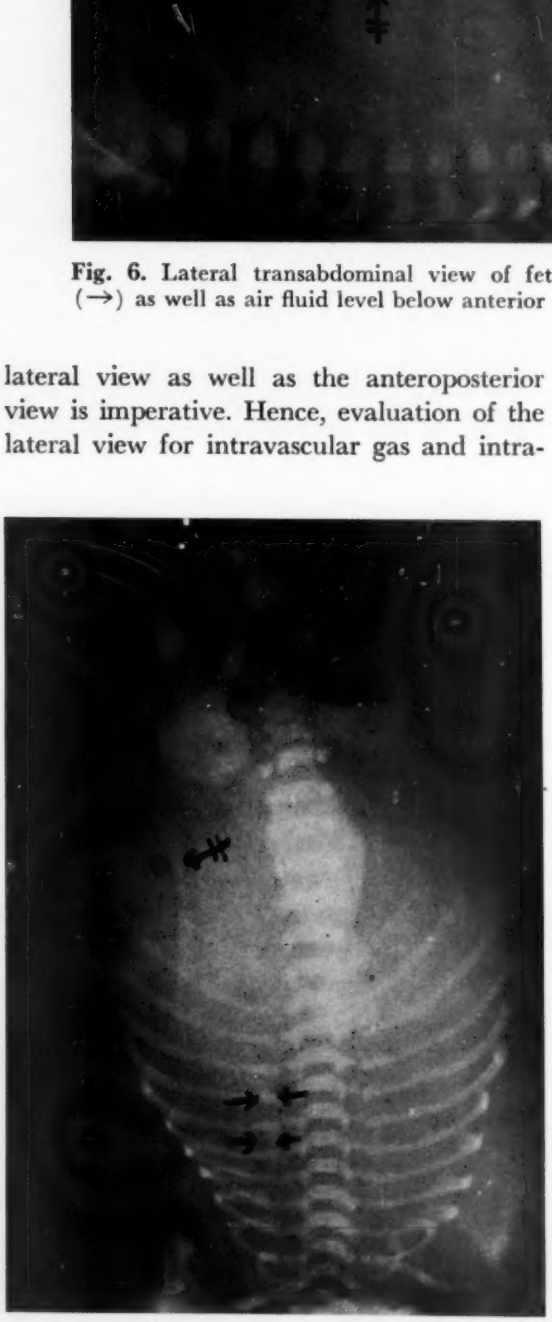


Fig. 7. Inverted anteroposterior view of fetus with air in inferior abdomen. (Site of abdominal gas bubble [⇛→] undetermined.)

Several cases in the literature note the presence of gas on one set of prenatal films, but its disappearance on subsequent studies prior to delivery. Since the origin and etiology of gas within the fetus are obscure, it would seem that the development of the gas is the result of the process of maceration after fetal death. Stewart and Hytten's[20] explanation that the gas, whether oxygen, carbon dioxide, or nitrogen, arises from some disintegration of the blood seems most logical. If, by experimental work, the timing of this disintegration can be ascertained, the optimum time for radiographic studies might be determined. This would increase the number of cases of fetal death diagnosed radiographically by intrafetal gas in utero, but the time of fetal death is still imponderable and difficult to determine with accuracy, thus, to a large extent, negating the possibility of accurate timing. Holm[9] attempted to evaluate the period of maximum gas formation. Further study of this factor would possibly yield the most optimum time of ordering films for a greater per cent of correct diagnosis.

It should be noted that, on the films of the stillborn fetus (Figs. 1-4), gas in the vascula-

ture was seen and confirmed at autopsy. This suggests that, when gas is present in extravascular sites, it is also intravascular, but not in sufficient amounts to be recognized. This would correlate with the 6 cases mentioned above where gas was demonstrated in both intravascular and extravascular sites within the fetus in utero.

Summary

1. A case is reported of intrauterine fetal death diagnosed by the presence of intra-abdominal fetal gas.

2. Intrauterine fetal gas, whether intravascular or extravascular, remains the one pathognomonic radiographic sign of intrauterine fetal death.

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CURRENT OPINION

Re-evaluation

Accuracy of colpomicroscopy of the cervix in the light of histopathologic examinations

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By the examination of the surface of the cervix, enlarged 140 to 270 times, trends in the development of epithelial processes may be examined. However, owing to the fact that in the colpomicroscopic picture the epithelium can only be seen for a depth of 70 μ, certain morphologic conditions, e.g., hyperactivity of the basalis, glandular epidermization, etc., are not visible. Similarly, a neoplastic change taking place in the deep layers of the epithelium or in the cervical canal cannot be observed by this method. The verification of the pathologist is therefore indispensable.

Material and terminology

The present study concerns 116 patients with cervical lesions examined both colpomicroscopically and microscopically. These examinations took place during the years 1956-1958 and the patients are still under observation. The colpomicroscopic examinations were made in our clinic and the pathologic specimens were studied in the laboratory of pathology.

The collected material is divided into four groups, as follows:

1. Normals and others, including hyperactivity of the basalis layer and leukoplakia, 7 cases.
2. Erosion of the portio vaginalis, 62 cases.
3. Erosion with "paratypia" of the epithelium, 13 cases.
4. Carcinoma of the portio, 34 cases.

The term "paratypia" was introduced by Laskowski to indicate cellular changes not yet characteristic of cancer. The paratypical changes present many different features, such as enlargement of the cells (macrocytosis), nuclear changes (macronucleosis, polynucleosis, and hypernucleosis) and the definitely atypical forms. According to the type of cellular changes and their frequency we may designate the "paratypia" as either of a low or high grade. In cases of paratypia of the lower grade the existence of carcinoma in the cervix is not very probable; in cases of paratypia of the higher grade the existence of malignant process in other areas of the same cervix cannot be excluded.

Cases in which paratypical cells are arranged in large groups and obscure the architecture of the epithelium, destroying its normal stratification, Laskowski refers to as "paraplasia." Paratypia and paraplasia are still reversible changes but they may sometimes be very similar to preinvasive carcinoma in their morphology. There are also borderline forms which constitute a transition from paraplasia to preinvasive cancer.

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The final pathologic diagnoses in these cases were reached through examination of the biopsy specimens and, in the cases of cancer, from the examination of operative material.

The colpomicroscopic diagnoses were established before biopsy specimen was taken. In interpreting the colpomicroscopic pictures the classification elaborated in our clinic by Widy and Szamborski was used. It is the only colpomicroscopic classification which corresponds with Papanicolaou's classification of the cytologic material. Our colpomicroscopic classification consists of four classes designated as follows:

I. The normal structure of the squamous epithelium of the portio vaginalis, as viewed from its surface.

II. Typical erosion, glandular and papillary, in the stage of epidermization.

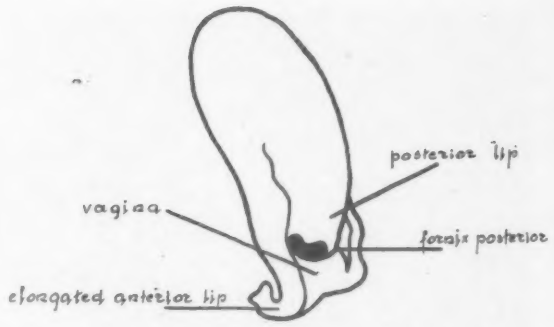


Fig. 1. Anatomic relationships explaining a false-negative report.

III. "Paratypia" of the epithelium.

IV. Carcinoma.

Group III of our classification corresponds to Grünberger's "pm" and "pchr" (polymorphia and polychromasia).

In the accompanying tables, the third group, paratypia, is subdivided into a lower

Table I. Colpomicroscopic and histopathologic diagnosis in 116 studied cases

	Colpomicroscopic diagnosis										
	Miscellaneous			*Erosion II*			*Paratypia III*			*Carcinoma IV*	
Histopathologic diagnosis	*Normal*	*Hyperactivity basalis*	*Leukoplakia*	*I to II*	*II*	*II to III*	*Lower grade (a)*	*Higher grade (b)*	*Probable carcinoma (c)*	*Squamous cell*	*Indefinite*
1. Miscellaneous											
a. Normal epithelium	2										
b. Hyperactivity basalis		1					1	1			
c. Leukoplakia			1					1			
2. Erosion											
a. True				1	3	2	1	6			
b. Glandular-papillary				2	10	6	8	17		2	
c. Semiepidermization											
3. Paratypia											
a. Lower grade					1		5	3			
b. Higher grade								2		2	
c. Probable carcinoma, preinvasive											
4. Carcinoma											
a. Preinvasive								1	5	8	
b. Invasive	1							4		10	4
c. Adenocarcinoma								1			

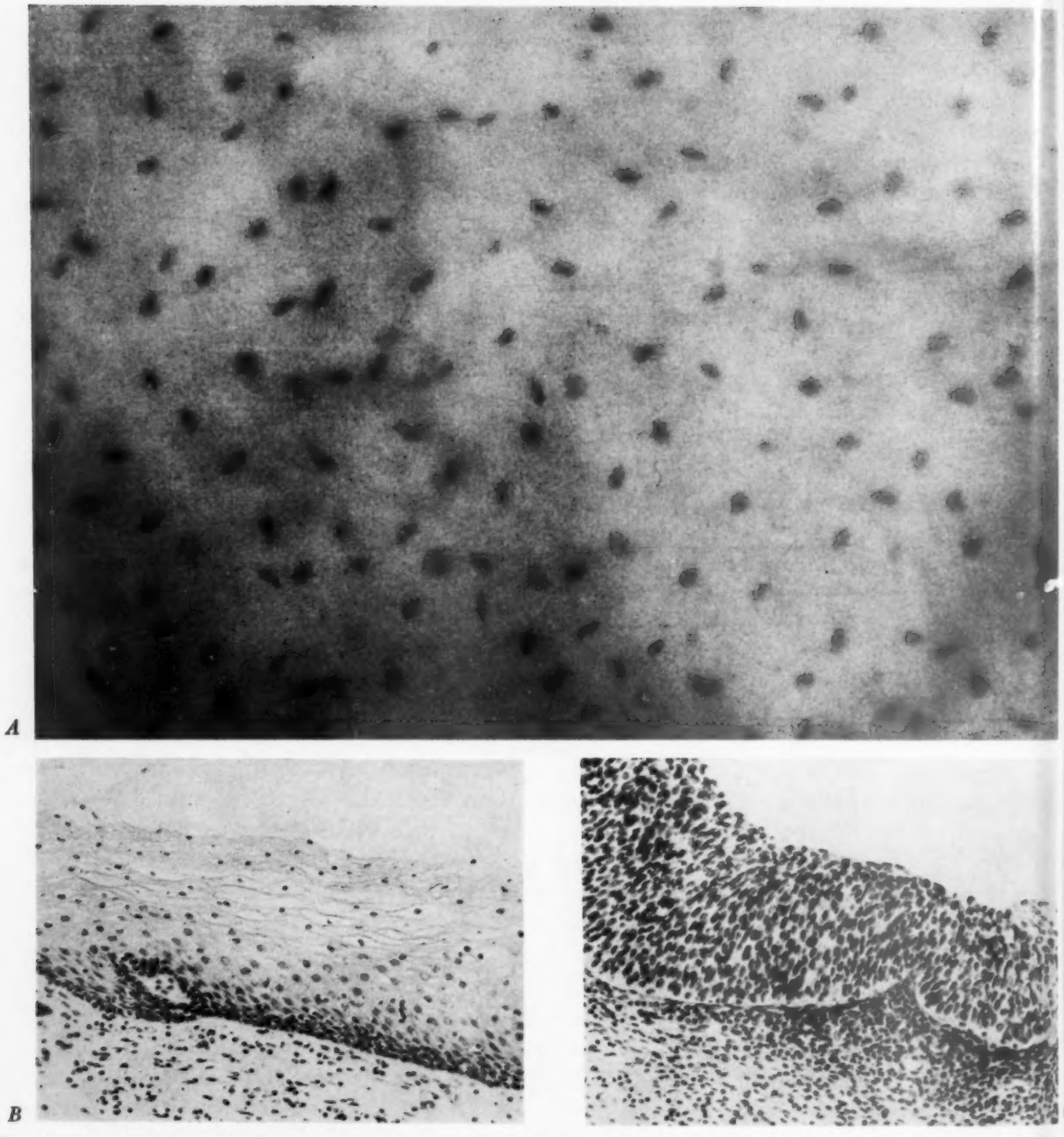


Fig. 2. *A*, Colpomicroscopic view in Case 102. (Courtesy of Dr. F. Widy.) *B*, Histopathologic section of area shown in *A*. *C*, An area from the malignant change of the posterior lip of the cervix.

grade, IIIa, a higher grade, IIIb, and "probable carcinoma," IIIc.

Table I presents our material divided according to histopathologic diagnoses and related to the original colpomicroscopic estimate of each case. Cases in which the colpomicroscopic diagnosis was exactly confirmed by the pathologic examination are grouped in this way in the areas within the heavy line. In cases outside this line there was a difference between the colpomicroscopic and histopathologic diagnoses.

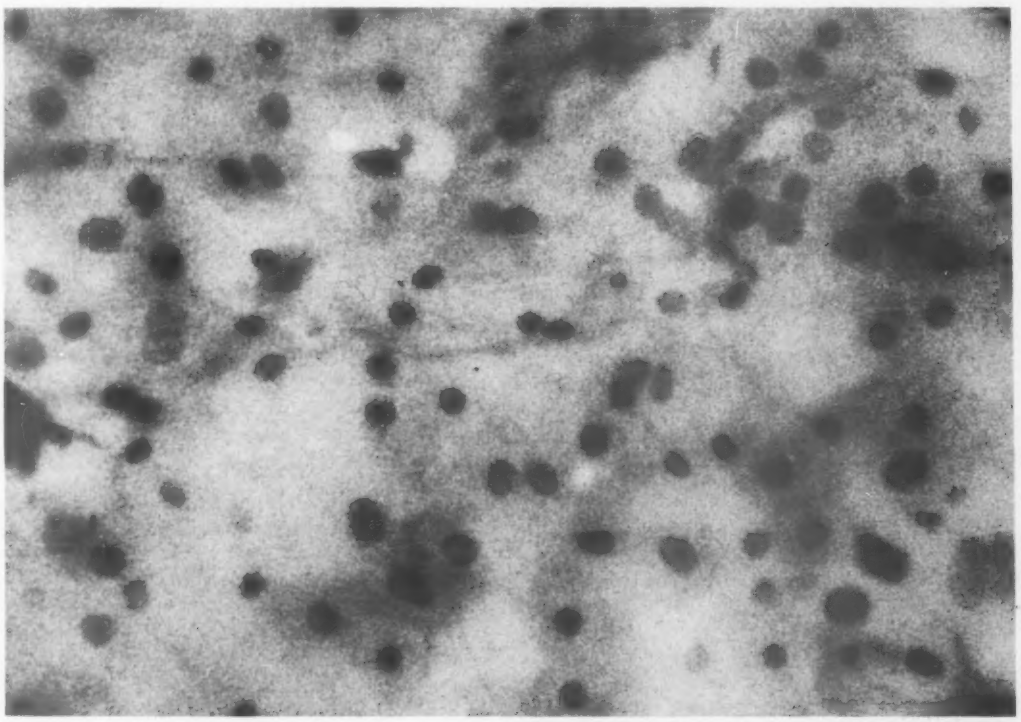
When the difference in colpomicroscopic and histopathologic diagnosis was only slight, had no significant bearing on the treatment, and did not expose the patient to the unnecessary taking of a specimen, this colpomicroscopic diagnosis was termed *inexact*.

When the colpomicroscopic diagnosis caused a clinical error which endangered or exposed the patient to an unnecessary operation, the diagnosis was called *erroneous*. The colpomicroscopic diagnosis which we have termed *false* was the most disadvantageous for the patient, for it consisted either in a colpomicroscopic failure to recognize a suspicious or definitely malignant process (false-negative) or characterizing benign changes as cancer (false-positive) (Table II).

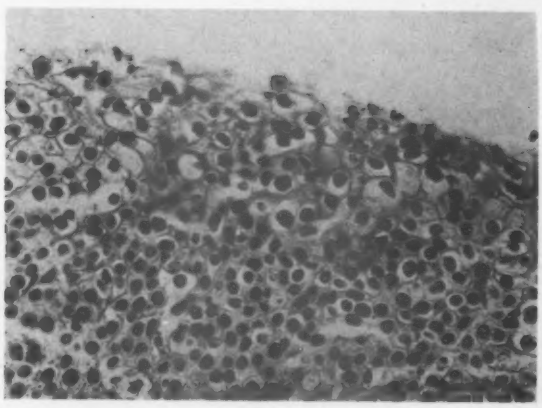
Results

As is shown by the chart, cases diagnosed pathologically as erosion had very often been previously designated colpomicroscopically as epithelial paratypia. Among the 13 cases eventually shown to be instances of paratypia, there was a fair degree of correspondence with the colpomicroscopic classification (Table II).

The material was found by histologic examination to include 34 cases of carcinoma. Four of these cases were so far advanced that the clinical diagnosis did not demand additional methods of examination. The colpomicroscopic appearance of these cervices was not typical of a neoplasmatic process but only of necrotic tissue. In Table II these cases have been placed in the in-



A



B

Fig. 3. *A*, Colpomicroscopic view in Case 111, established inexactly as "probable carcinoma." (Courtesy of Dr. F. Widy.) Histopathologic diagnosis was carcinoma, preinvasive. *B*, Histopathologic section of area shown in *A*.

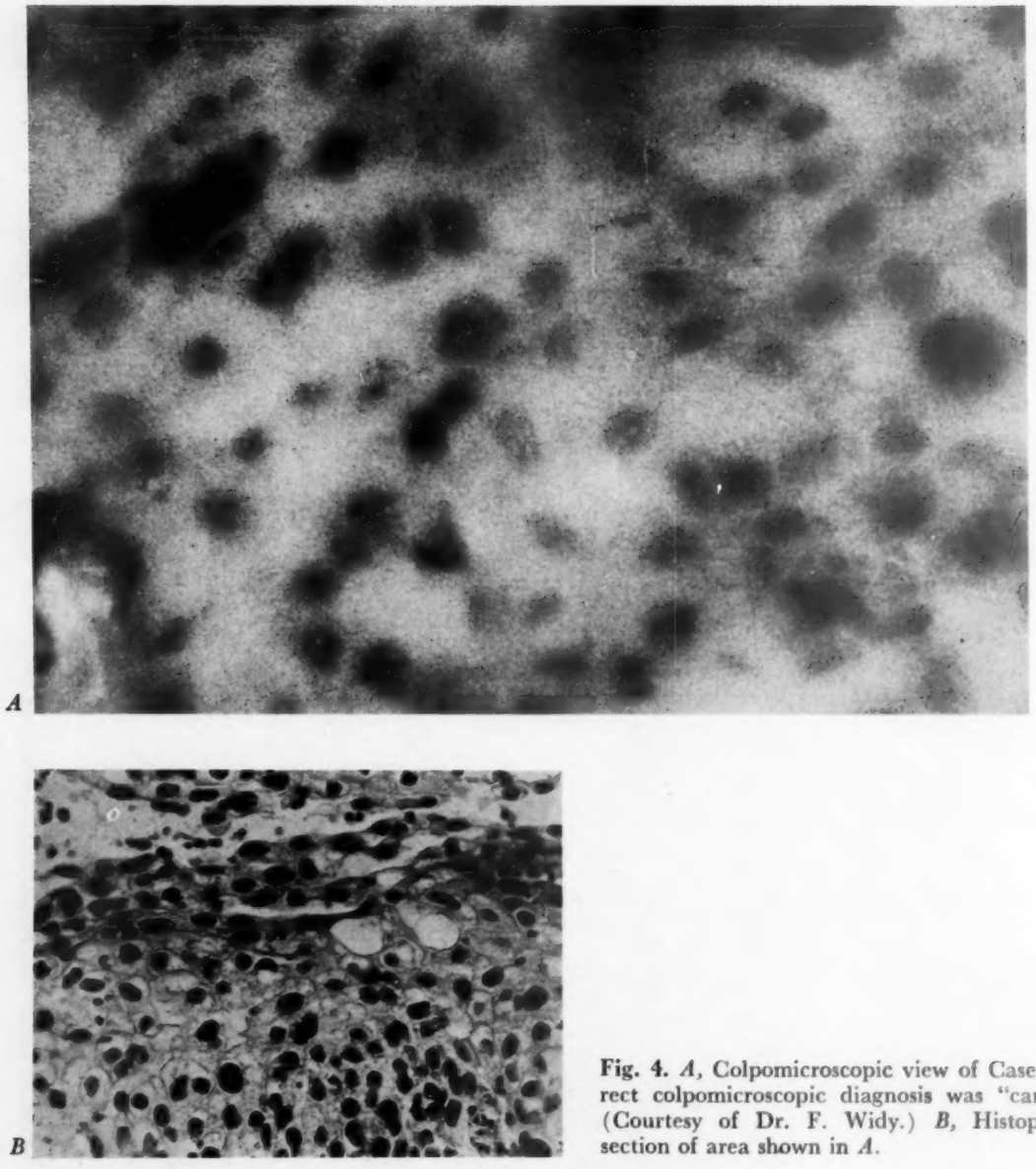
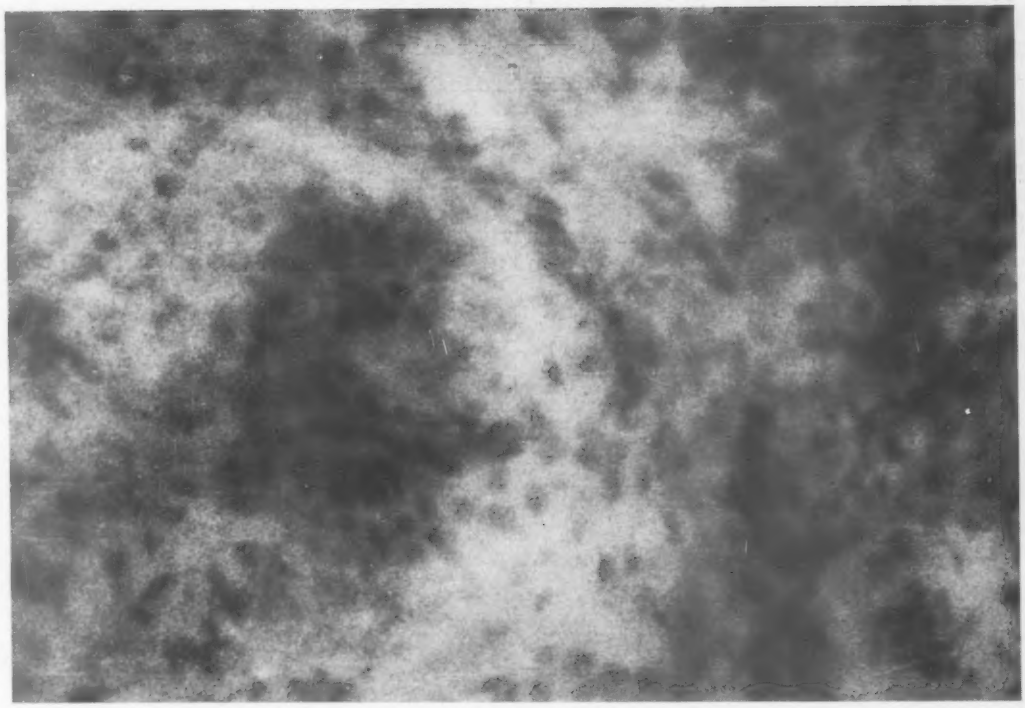


Fig. 4. *A*, Colpomicroscopic view of Case 55. Correct colpomicroscopic diagnosis was "carcinoma." (Courtesy of Dr. F. Widy.) *B*, Histopathologic section of area shown in *A*.

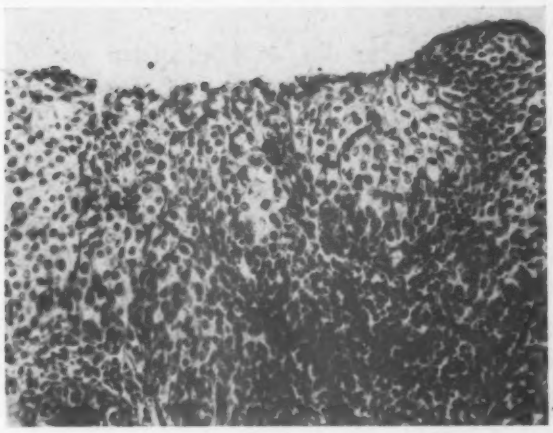
definite column. The remaining cases of carcinoma include: 14 cases of preinvasive carcinoma, 15 cases of invasive squamous carcinoma, and 1 case of adenocarcinoma.

The single case of cancer missed by colpomicroscopy had been designated as normal epithelium. The carcinoma was later found localized around the external os and on the posterior lip of the cervix. Fig. 1 explains the cause of the false-negative colpomicroscopic diagnosis. Fig. 2, A, B, and C are the colpomicroscopic and histologic pictures of this case.

There was only one case of adenocarcinoma of the cervix in our material. The cytologic examination of this case showed the presence of suspicious cells. The colpomicroscopic appearance was described as follows: "Around many glandular openings there is marked hyperchromasia and polymorphia of the epithelial cells." This report induced the gynecologist to take a biopsy specimen. Histopathologic examination of this tissue showed adenocarcinoma. Since the usual gynecologic examination had disclosed no change of the portio typical of neoplasm, the colpomicroscopic and the cytologic examinations were crucial in this case.



A



B

Fig. 5. *A*, Colpomicroscopic view of another type of cervical carcinoma (Case 4) diagnosed correctly. (Courtesy of Dr. F. Widy.) *B*, Histopathologic section of area shown in *A*.

Under a miscellaneous heading (Table I), 3 cases are described as showing basal hyperactivity and 2 leukoplakia in the histologic view. Two cases of the former group were designated by the colpomicroscopic examination, inexactly as paratypia and 1 case, erroneously as normal epithelium. In the cases of leukoplakia 1 colpomicroscopic diagnosis was correct and the second inexact.

Comment

During the study of the accuracy of colpomicroscopy it was shown that a classification of the colpomicroscopic diagnoses, based on ultimate histopathologic verification, into four grades, i.e., "correct," "inexact," "erroneous," and "false," is very useful. The morphologic patterns, like the equivalent biologic processes, are not isolated states but are indices of complex changes which follow each other transitionally, through the stages of inflammation, epidermization, paratypia, and paraplasia, to malignant growth. These stages are often difficult to differentiate by the histopathologist and are even more difficult with the colpomicroscopic examination.

The colpomicroscopic designations "er-

Table II. Degree of difference between histologic and colpomicroscopic diagnoses

Histopathologic diagnosis		*Colpomicroscopic diagnosis*				
		Correct	*Inexact*	*Erroneous*	*False*	*Indefinite*
Erosion	62	24	9	27	2	
Paratypia of epithelium	13	7	4	2		
Cervical carcinoma	34	18	5	6	1	4
Normal and other	7	3	3	1		
Total	116	52	21	36	3	4

roneous" or "false" have an obviously important significance for the clinic. An inexact designation should attract the attention of the physician using the colpomicroscope and help him to make a correct diagnosis of the next case.

The difference between the colpomicroscopic and histopathologic results may be due to two factors:

1. Differences due to the method, to limitations inherent in the instrument, or to technical difficulties arising from anatomic changes.

2. Differences due to inadequate use of the colpomicroscope (or lack of precision in taking the biopsy) or due to incorrect interpretation of the colpomicroscopic pictures.

In the material presented, the number of inaccuracies due to the first group of causes is less than the number in the second group. To the first group 7 cases belong: 4 cases of advanced cervical cancer covered by necrotic masses of tissue, 1 case of nondiagnosed cancer, 1 case of adenocarcinoma, and 1 case of basal hyperactivity.

The remaining 57 cases belong to the second group. These were diagnosed: Inexactly, erroneously, and falsely. Our chart shows that the false or erroneous diagnoses occurred almost entirely in the first 78 cases. All cases thereafter except for the hundred and second were diagnosed correctly or simply inexactly. The longer the physician used the colpomicroscope the better he recognized the colpomicroscopic pictures. The greater the experience, the smaller the number of cases diagnosed erroneously.

Summary

1. One hundred and sixteen sections of cervices previously evaluated colpomicroscopically were examined histopathologically. Among these were 34 cases of cervical cancer.

2. Three (2.58 per cent) colpomicroscopic diagnoses were false; 36 (31 per cent) were erroneous.

3. In 7 cases the limited functioning of the instrument was the source of error. In 57 incorrect diagnoses, wrong interpretation of the colpomicroscopic pictures was the cause.

4. A third of the cases presented were diagnosed correctly owing to the use of other methods besides the colpomicroscope.

5. The number of erroneous diagnoses became less as the experience of the physician serving the colpomicroscope grew.

Conclusions

The analysis of the data from the material presented shows that the diagnoses in about two thirds of the patients examined colpomicroscopically were established correctly or no more than incorrectly. In the remaining third (diagnosed falsely or erroneously) one may reach the correct diagnosis by other methods, such as by cytologic or histopathologic examination. We believe the point of view of such authors as Antoine or Wolfe, who think that colpomicroscopy should widen the possibilities of cooperative methods and thus lead to a more precise diagnosis, is right.

Colposcopic findings in carcinoma in situ

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IN RECENT years cytology has become increasingly important for the early diagnosis of carcinoma in women. In Germany, however, colposcopy[13] seems to have been successfully employed for a long time to accomplish the same purpose. It is the belief of many authors that one can eliminate with the colposcope the normal cases without overlooking any malignant lesions.[6, 7, 10, 12, 16, 17] Obviously the use of the colposcope is limited to the visible part of the cervix uteri and alterations in the cervical canal cannot be seen.[5, 14, 18, 22, 26] Discovery of intracervical carcinoma with its early lesion requires the use of cytologic methods. Recently, investigators at the University Hospital of Gynecology and Obstetrics in Graz have questioned the reliability of colposcopic examination of the surface of the portio vaginalis as a means of eliminating benign transformations. These workers employed both cytology and colposcopy in their studies.[4, 5]

The object in the present work was to compare colposcopic findings with the results of cytologic diagnosis and histologically proved cases of carcinoma in situ.*

Material and methods

The histologic pictures of 105 cases of carcinoma in situ and so-called microcarcinoma were compared with the preoperative colposcopic findings. The diagnosis of all cases was based on cytologic studies. The lesions were excised either by conization of the cervical canal or by vaginal hysterectomy. The histologic section included the entire gross specimen.

Schematic sketches were made from the histologic and colposcopic pictures and associated in three-dimensional drawings with vertical and horizontal projection. The material was grouped according to the histologic localization of the carcinoma in situ beginning with the most peripheral at the surface of the cervix and ending with the highest intracervical. Fig. 1 is an illustration of one of these sketches, and Fig. 2 gives 6 examples which are representative of our results.

The histologic findings showed mostly carcinoma in situ with or without early stromal invasion[2, 9] and so-called microcarcinoma, with more advanced stromal invasion (Groups 4 and 5 of Hamperl[11]). The "microcarcinomas" are similar to Group Ia of Blaikley, Kottmeier, Martius, and Meigs.[3]

We differentiated, employing the usual colposcopic terminology: *positive,* adaptive vascular hypertrophy, "corkscrew capillaries," nodulated carcinoma tissue; *suspicious,* matrix areas, atypical transformation zone; and *normal,* normal squamous epithelium, ectopic epithelium with or without a marginal transformation zone, open, closed, and vascular transformation zone. The youngest patient was 19, the oldest 64. The average age was 39.8 years.

Results

Comparing 105 histologically proved carcinomas in situ with the preoperative colposcopic findings there were only 60 cases (57.14%) colposcopically positive or suspicious. In 45 cases there was no suspicion

From the Universitäts-Frauenklinik.

**Detailed report in Kern and Bötzelen, Arch. Gynäk., 1961.[15]*

Table I. Colposcopic findings in 105 patients with histologically proved early lesions

Suspected carcinoma, adaptive vascular hypertrophy	*Matrix areas*				*Matrix-like*	*Atypical transformation zone*
	Mosaic leukoplakia	*Ground leukoplakia*	*Leuko-plakia*	*Combination of matrix areas*		
9	6	10	9	11	10	5
60 (57.14%) Colposcopic positive or suspicious						

of carcinoma in situ by previous colposcopic examination. Table I gives our results.

Carcinoma in situ with colposcopic positive or suspicious findings (60 cases). The degree with which the colposcopic report coincided with the histologic picture was studied. In 42 of 60 cases the findings coincided in general, but the areas were not always of the same size. The histologic lesion may have been smaller than the colposcopic findings, or the reverse. Only 16 of these 42 cases agreed precisely and of these 16 cases 9 were diagnosed as positive (Fig. 2, *a*) by colposcopic examination.

In 18 of 60 cases there was no topographic correlation of the colposcopically suspicious area and the histologic lesion. The colposcopically detected transformation, however, occurred in the neighborhood of the histologically proved carcinoma in situ (Fig. 2, *b* and *c*) and in no case were the areas widely separated. For example, there was no instance in which a colposcopically suspicious area was observed on the posterior cervical lip and the carcinoma in situ on the anterior cervical lip. Of particular interest were 11 of these 60 cervices, which showed a colposcopically suspicious area on one cervical lip, while the carcinoma in situ was found to involve both lips.

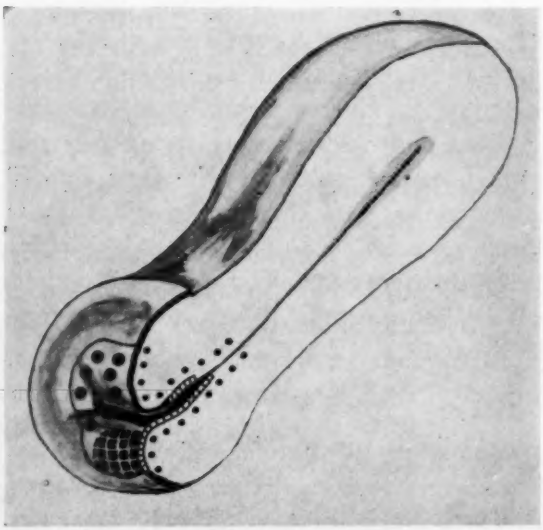


Fig. 1. Topographic correlation of histologic and colposcopic findings. (For explanation of symbols see Fig. 2.)

Carcinoma in situ with colposcopic normal findings (45 cases). In 45 patients the colposcopic findings were completely normal (Table I). These cases were discovered as a result of Class IV and V of Papanicolaou cytology smears and were histologically proved (Fig. 2, *e* and *f*). In 11 of these 45 cases the lesions were restricted to the cervical canal (Fig. 2, *f*), but in 34 they were found on the surface of the cervix (Fig. 2, *e*).

The relation of the localization of the carcinoma in situ as determined by histologic examination to that reported from the colposcopic examination is shown in Fig. 3.

Comment

From the 60 cases of carcinoma in situ in which colposcopic examinations had shown positive or suspicious areas, we are able to draw the following conclusion: A positive colposcopic diagnosis based on the presence of nodulated carcinoma tissue, corkscrew capillaries, and the adaptive vascular hypertrophy (synonym, IVa area of Hinselmann) showed a striking topographic consistency with the histologic findings. In every such case a positive cytologic smear and histologically atypical epithelium has been found.[14, 26]

Vascular transformation zone	*Open and closed transformation zone*	*Ectopic epithelium with marginal transformation*	*Normal squamous epithelium*	*Total*
12	27	3	3	105
		45 (42.86%) Colposcopic normal		

No such close correlation was seen between suspicious colposcopic findings, such as matrix areas and atypical transformation zones, and the histologic lesions. These findings are not surprising in view of the observations of Zinser[25] and others[5, 8, 17, 22] who by colposcopic examination observed, from nonselected material, a 10 to 15 per cent incidence of suspicious areas but found only a 10:1 index of malignancy. It is well known that these matrix areas may change during a period of observation and even disappear.[7, 25]

Generally speaking, colposcopically suspicious transformations lay within the region or adjacent to the histologically proved carcinoma in situ. The pathologic epithelium at the surface of the cervix generally reaches the external os, while the matrix areas usually occur peripherally (Fig. 2, *b*). Carcinoma in situ restricted to the cervical canal frequently shows some suspicious colposcopic areas around the external os and even at the cervical surface. In these cases the colposcopic finding can be regarded as an indicator of an early lesion elsewhere at the cervix uteri.

Wedge or punch biopsies have been frequently recommended during colposcopic examination.[24] However, in order to demonstrate correlations between the suspicious colposcopic area and a histologically positive field, it is necessary to take a large number of such biopsies. In the present material proved positive by cytology, biopsies with malignant lesions could be expected in all cases with positive colposcopic findings but only if the excision extended to the external os.

Any biopsy will fail in cases where the lesion is restricted to the cervical canal. In such cases a careful cervical curettage provides a better chance of success than a biopsy. A cervical curettage does give a considerable degree of security in excluding an invasive carcinoma located in the cervical canal. However, with any kind of biopsy there remains an element of uncertainty as to the type of tissue adjacent to the excision.[23] To eliminate such an uncertainty we usually treat cytologically positive patients with a

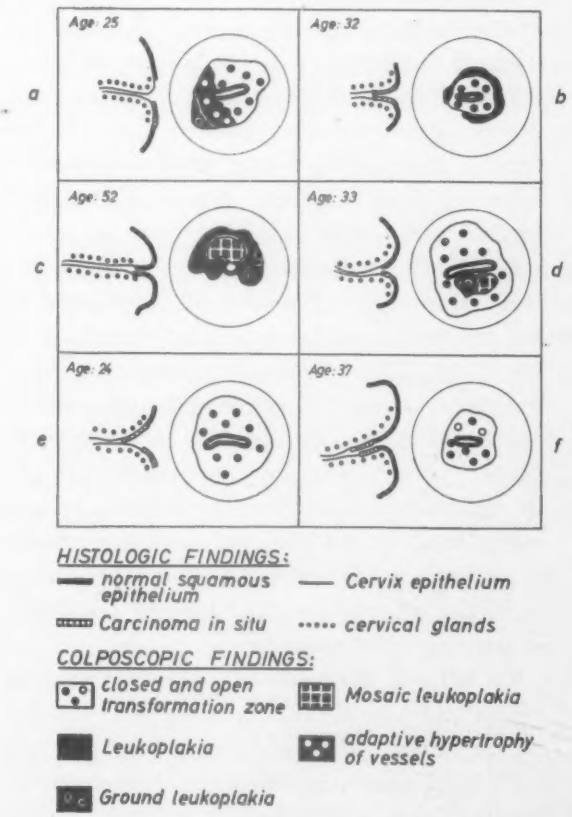


Fig. 2. Some characteristic colposcopic and histologic findings.

December, 1961
Am. J. Obst. & Gynec.

histological localization (105 cases)	Colposcopic findings: positive	suspicious	normal
(21 cases)	0	10	11
(84 cases)	9	41	34
total	60		45

Fig. 3

widespread conization. Our special histologic work-up[19, 20] of this excised tissue makes it possible to survey the entire cervical canal and the cervical surface and determine the exact location of the entire lesion. The incision line of the cone is routinely placed peripheral to the cervical gland field or the iodine negative zone at the cervical surface.

In postmenopausal patients or in patients of childbearing age where additional findings such as fibromyoma of the uterus, endometriosis, inflammatory adnexa diseases, and descensus uteri occur, hysterectomy is preferred, after invasive carcinoma is excluded by a cervical curettage. Frequently vaginal hysterectomy is performed.

Of the 45 patients who were colposcopically normal, 11 showed lesions localized in the cervical canal and 34 at the surface of the cervix. The failure of colposcopic examination to reveal lesions located in the cervical canal is not astonishing. A completely normal cervical surface may even be present in macroscopically developed intracervical carcinoma. In all patients with carcinoma in situ one has to reckon with a 20 per cent incidence of intracervical lesions, especially in patients older than 40.

Of utmost importance is the fact that in 34 patients with carcinoma in situ situated on the surface of the cervix, the colposcopical report was not suspicious. Moreover, in another 11 cases, previously referred to, the carcinoma in situ extended to both lips but was colposcopically suspicious in only one lip. Table I shows that practically no colposcopic report can positively exclude a malignant lesion. In this regard our results agree with those of Burghardt and Bajardi[5] but are in disagreement with the interpretation of many other authors.

The fact that 40.5 per cent of cytologically discovered and histologically proved carcinomas in situ involving the cervical surface are colposcopically normal should not be surprising, for the structure of the surface is not changed very much by the intraepithelial lesion. The normal squamous epithelium is replaced by an epithelium without stratification, with densely packed nuclei and numerous partly atypical mitoses, and is without intracellular spaces. Only rarely can one recognize with the microscope a special vascularization in the subepithelial layer and in many cases the intraepithelial lesion imitates the transformation shape of normal squamous epithelium.

When one looks with the colposcope, using front light illumination, at an epithelium which shows only a certain color change due to the more dense microscopic structure, one cannot recognize the histologic characteristic qualities of carcinoma in situ. The microcolposcopy of Antoine and Grünberger,[1] with the higher magnification of 110 to 280 diameters, may give somewhat better results.

It is not possible to answer the question as to whether the iodine test would have given positive findings in our 34 colposcopic "silent" cases or not. This question will be considered in future studies. It is purely noteworthy that Limburg in 1956 made 122 biopsies from 34 iodine negative areas without observing malignant lesions.

It may be argued that if such a high rate of detection failure, as a result of false negatives, had occurred in routine clinical examination, the fact would have been revealed in time by the appearance of true carcinoma. It must be remembered, however, that while the period required for the evolution of carcinoma in situ to true carcinoma is unknown, it is probably very long. Ober, Kaufmann, and Hamperl[21] have reported that the transformation of the microscopic picture from

simple anaplasia to true clinical carcinoma may cover a span of 15 years.

Numerous cases of carcinoma in situ will be overlooked as a result of a colposcopically negative examination, since these cases will not attract attention even in repeated examinations. The colposcope is a reliable instrument for diagnosing true carcinoma. The colposcope also has a value in examining the physiologic changes of the squamocolumnar junction during a woman's lifetime and for observing inflammatory reactions and their healing. It cannot, however, be relied upon as an absolute diagnostic aid for carcinoma in situ.

Summary

The histologic pattern of 105 cases of carcinoma in situ and microcarcinoma were compared with the preoperative colposcopic findings. Schematic drawings in three dimensions were prepared from the histologic sections and the colposcopic appearance, and the material was classified according to the histologic sites of the in situ lesion. These investigations led to the following results:

1. Sixty cases (57.14 per cent) appeared colposcopically positive or suspicious; 45 cases (42.86 per cent) did not arouse any suspicion on colposcopic examination.

2. The colposcopic positive or suspect areas were situated in the region of the histologic changes or in their neighborhood. Close topographic correlation occurred in cases where the colposcopic findings suggested carcinoma or adaptive vascular hypertrophy. Early cases originating within the cervical canal did not yield positive findings on the surface of the portio vaginalis.

3. Among 60 colposcopically suspected or positive cases 11 showed histologic carcinoma in situ in the anterior and posterior lips whereas colposcopically abnormal findings were restricted to one lip only.

4. Forty-five cases of carcinoma in situ or microcarcinoma had normal colposcopic appearances (normal squamous epithelium, ectopic epithelium with marginal transformation, open, closed, and vascular transformation zones). Eleven of these lesions were situated in the cervical canal and 34 on the surface.

5. The diagnostic value of colposcopic findings is discussed. Uneven carcinomatous tissue and adaptive vascular hypertrophy always yield adequate cytologic and histologic findings. The index of malignancy in matrix areas and atypical transformation zones is, however, only approximately 10:1. Occasionally these areas can be regarded as indicators of an early lesion in adjacent sites. The chance of successful biopsies is discussed in the light of the presented material.

Conclusion

It must be concluded from our investigations that negative colposcopy findings do not exclude carcinoma in situ. Not only intracervical lesions but also a major part (40.5 per cent) of cytologically detected early cases of the portio vaginalis are colposcopically unrecognizable.

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Edited by
LOUIS M. HELLMAN, M.D.

Selected abstracts

New England Journal of Medicine
Vol. 264, March 23, 1961.

*Johnston, Alan W.: Chromosomes in a Child With Mongolism and Acute Leukemia, p. 591.

Johnston: Chromosomes in a Child With Mongolism and Acute Leukemia, p. 591.

The chromosome complement of the patient with Mongolism and untreated acute leukemia is described. The basic number was 47, with trisomy of chromosome No. 21. Abnormalities of chromosome number, fragments, and breaks were found in 8 cells. That the fragmentation abnormalities and chromosome breaks are evidence the cells are leukemic in origin is suggested by the complete absence of abnormalities during the remission induced by therapy. The bone marrow specimens on which this study was based showed a marked paucity of mitoses on culture. The author points out that the number of cases of aneuploidy associated with leukemia or other malignant processes suggests that there may be a common basis for the association of Mongolism and leukemia. The theory is stated that perhaps because of the aneuploidy of Mongolism there is an unstable genome rendering autonomy of the cell more likely to develop and that the evidence of this is leukemia.

Douglas M. Haynes

April 20, 1961.

*Friedell, G. H., Cesare, F., and Parsons, L.: Surgical Treatment of Cancer of the Cervix Recurring After Primary Irradiation Therapy, p. 781.

*These articles have been abstracted.

Friedell, Cesare, and Parsons: Surgical Treatment of Cancer of the Cervix Recurring After Primary Irradiation Therapy, p. 781.

The authors report on 109 patients subjected to either Wertheim hysterectomy and bilateral pelvic lymph node dissection or pelvic exenteration during the years 1948 through 1958 following recurrence of carcinoma of the cervix after primary irradiation therapy. The youngest patient was 29, the oldest 59, with an average age of 50 years. Eighty-five per cent of the patients were between 35 and 59 years of age at the time of operation. The interval between radiation therapy and radical operation ranged from 6 months to 21 years. Twenty-seven patients were treated by Wertheim hysterectomy and bilateral pelvic lymphadenectomy, while 82 patients with more extensive tumor had pelvic exenteration. Ten, or 43.5 per cent, of 23 patients treated by Wertheim hysterectomy had positive lymph nodes as did 32, or 42.1 per cent, of 76 treated by exenteration. Preoperative findings which served as contraindications to radical operation included positive lymph nodes in groin or supraclavicular area, edema of the thigh or leg, back pain radiating down the leg, roentgenologic evidence of distant metastases, advanced age, and patient reluctance. Radical Wertheim hysterectomy was performed in those patients in whom the tumor was confined to the cervix and uterus with or without minimal paracervical involvement. With invasion of bladder or rectum or both, either a partial or total pelvic exenteration with ureteroenterostomy (sigmoid or ileal bladder) is considered indicated.

Of 76 patients with cancer in the surgical specimens operated on 5 or more years before this report, 25 (31.3 per cent) survived for 5 or

more years. This figure included 13 of 20 patients in the Wertheim group and 12 of the 56 in the extenteration group. Nine of the latter 12 patients are alive and well 6 to 10 years later, 2 have survived for 5 years and 1 died 7 years after operation. None of the 25 patients with exenteration and positive lymph nodes survived for the 5 year period. For patients with negative lymph nodes and cancer in the surgical specimen the 5 year survival was 50 per cent. Five or more years after operation 38.7 per cent of 31 patients with exenteration and 81.8 per cent in Wertheim group survived. Twenty of 109 patients died within 30 days after operation (surgical mortality of 18 per cent). One death occurred in the Wertheim group, and 19 followed exenteration. The most common complications were those involving the urinary tract. There were 4 urinary fistulas in the Wertheim group and 6 after exenteration (over-all incidence of 9 per cent). Other complications included wound dehiscence, perineal hernia, and severe postoperative hemorrhage. Late in the course in 15 cases, pyelonephritis amenable to the therapy developed. Factors influencing the prognosis included size of tumor at the primary site, the presence or absence of lymph node metastases in surgical specimen, and the fact that the patients were being treated for recurrent cancer after primary radiation.

Douglas M. Haynes

May 11, 1961.

Simkin, Benjamin: Urinary 17-Ketosteroid and 17-Ketogenic Steroid Excretion in Obese Patients, p. 974.

New York State Journal of Medicine

Vol. 61, Jan. 1, 1961.

*Nesbitt, R. E. L., Jr., and Cirigliano, G.: Use of Relaxin During Parturition, p. 90.

Nesbitt and Cirigliano: Use of Relaxin During Parturition, p. 90.

The authors present observations concerning the value of relaxin during parturition in patients at term. A carefully controlled study of a purified brand of relaxin (Cervilaxin) was carried out in an effort to determine its effect on normal term labor. This double-blind study was designed specifically to test the hypothesis that relaxin softens the cervix and thereby facilitates delivery and shortens time in unstimulated labor. One hundred and two presumably normal parturient women, who had established labor spontaneously, were selected at random from the clinic population when they were admitted to the labor suite. The consistency, effacement, and dilatation of the cervix were determined by sterile vaginal examination in each case. All patients were examined by the same investigator to rule out differences in the interpretation of the status of the cervix. Relaxin (2 ml. or 40 mg.) or a placebo was administered intravenously as soon as normal, strong, rhythmic contractions were established and effacement (approximately 75 per cent) and dilatation (3 cm.) of the cervix were far enough advanced to rule out prodromal labor. In the dosage administered and under the experimental conditions set for this clinical study it was observed that relaxin was not effective in speeding parturition in patients at term, regardless of parity or cervical dilatation at the time of administration. The hormone demonstrated nothing of clinical value that justified its continued use during labor.

Reuben H. Adams

Feb. 1, 1961.

*Moya, Frank: Use of a chloroform Inhaler in Obstetrics, p. 421.

Moya: Use of a Chloroform Inhaler in Obstetrics, p. 421.

The author presents preliminary observations on the use of a precision vaporizer (Experimental Tecota Chloroform Inhaler) in obstetrics. Only analgesia levels were studied although the inhaler is capable of producing anesthetic concentrations of chloroform. No attempts were made to evaluate anesthetic planes of the agent. A total of 361 vaginal deliveries were studied. Of these, 161 were performed under chloroform analgesia, and 200 (controls) under nitrous oxide analgesia. Patients were chosen at random and were unselected except for the following: the use of chloroform was limited to ward cases and avoided in patients with a history of toxemia of pregnancy or liver disease. The use of the inhalation analgesia techniques was limited to continuous administration during the final portion of the second stage of labor and was terminated within a few minutes following birth. The total length of time on the inhaler was restricted to a maximum of 45 minutes and preferably less than 30 minutes. There were no intra- or postpartum complications which could be related to the use of either of the agents, and there were no maternal deaths. Serious cardiac arrhythmias or hypotension were not observed

in the 361 patients. Both techniques were found to be effective in producing demonstrable analgesia in 90 per cent of the cases. However, chloroform had a significantly greater incidence of complete relief of pain. Biochemical analyses of maternal arterial and umbilical cord blood samples showed no appreciable difference between the two agents. The condition of the infants at birth bore no apparent relation to the type or duration of analgesia. It is concluded that chloroform, when administered as described with this vaporizer, is a safe, simple, and effective means of producing maternal pain relief with no apparent depression of the infant.

Reuben H. Adams

Proceedings of the Society for Experimental Biology and Medicine

Vol. 104, No. 3, July, 1960.

*Damm, H. C., and Turner, C. W.: Extraction and Concentration of Mammogenic Fractions From Anterior Pituitary Gland, p. 472.

Damm and Turner: Extraction and Concentration of Mammogenic Fractions From Anterior Pituitary Gland, p. 472.

Methods are described for the extraction and concentration of fractions from the anterior pituitary gland which in intact male albino mice or ovariectomized female mice exhibit marked mammogenic properties. It would appear from this work that a separate specific mammogenic hormone exists and that the usual methods employed for the preparation of lactogen are not specific enough to eliminate the mammogenic factor.

J. Edward Hall

Proceedings of the Staff Meetings of the Mayo Clinic

Vol. 36, No. 2, Jan. 18, 1961.

*Pratt, J. H.: The Colon in Vaginal Reconstructions, p. 34.

Pratt: Colon in Vaginal Reconstructions, p. 34.

Four patients who have been operated on in recent years at the Mayo Clinic illustrate some of the various methods and circumstances under which the colon can be utilized to form a satisfactory vagina.

In congenital absence of the vagina the tissues are clean and healthy, the blood supply is good, and rapid healing and uncomplicated postoperative convalescence can be expected. When loss of the vagina follows operation or irradiation for a malignant lesion or resulting complications, the tissues have been damaged, and the blood supply may be, but usually is not, normal. Healing is often delayed and difficulties with infection, separation of sutures, and fistulas can complicate the postoperative period, and multiple operations may be necessary to effect a cure. The part of the bowel of choice for this maneuver is the sigmoid. It is adjacent to the vaginal tract. The blood supply with marginal vessels makes it possible to isolate a portion of sigmoid and when one end of the segment is passed down into the vaginal tract it carries its own blood supply with it. Intestinal continuity can be reestablished by an end-to-end anastomosis usually without a transverse colostomy.

The new vagina offers additional rehabilitation to such patients and may well make the difference between a normal, well-adjusted patient and one who feels that perhaps the cure is almost as bad as the disease. The risk nowadays is minimal and under these circumstances surgeons should feel justified in attempting such reconstruction if it is at all possible.

Edward Solomons

No. 8, April 12, 1961.

Waddell, Kenneth E., Hunter, James S., Jr., and Berman, Stanley: Rupture of Dermoid Cyst of the Ovary During Pregnancy, p. 214.

Revista Colombiana Obstetricia y Ginecologia

Vol. 11, No. 2, April–May, 1960.

*Paz, F. C.: Pregnancy and Hansen's Disease, p. 267.

Paz: Pregnancy and Hansen's Disease, p. 267.

The author concludes after studying 217 cases that Hansen's disease has no apparent effect on pregnancy; pregnancy, on the other hand, can adversely affect the leprous lesions. He also feels that during pregnancy one frequently sees relapses but that labor has no effect on the lesions. However, during labor one does see cervical dystocia characterized by rigidity.

Francis B. O'Brien, Jr.

No. 3, May–June, 1960.

*Montoya, M. G.: The Increase in the Blood Platelets Determined by Serial Counts as an Indication of Ovulation, p. 372.

Montoya: Increase in Blood Platelets Determined by Serial Counts as an Indication of Ovulation, p. 372.

The author studied 30 patients in order to determine the reliability of serial determinations of blood platelets. This was correlated with serial measurements of the basal body temperature and crystallization of the cervical mucus. The author feels that there is a characteristic rise in the serial platelet count followed by a drop below this level in the middle of the cycle. In correlating this, she feels that this is a relatively secure test as an indication of ovulation. All cases were also studied at the time of menstruation or just before by endometrial biopsy in order to confirm the occurrence of ovulation. The author also studied 4 patients in whom there was no evidence of ovulation by any of the test methods and found no characteristic rise in platelets. *Francis B. O'Brien, Jr.*

Southern Medical Journal

Vol. 54, No. 4, April, 1961.

*McNally, H. B., and Fitzpatrick, V. D.: Patients With Four or More Cesarean Sections: Second Series, p. 360.

*Haynes, D. M., and Clemmons, H. L.: Cesarean Section: A Six Year Review, p. 369.

*Chatham, B. C.: A Ten Year Experience With Cesarean Section in a 50 Bed Hospital, p. 374.

McNally and Fitzpatrick: Patients With Four or More Cesarean Sections, p. 360.

A second study of patients having 4 or more cesarean sections is presented. The 710 patients in the present series are compared with 130 patients reported in 1955. The information was obtained by sending a questionnaire to various hospitals in the United States and Canada.

The two series are quite comparable in most aspects measured. Of particular interest is the observation that in both series the number of pregnancies drops sharply after the fifth section. That this is due to diminished fecundity cannot be inferred from present data.

Fetal loss was found to be no greater in sections of high parity than in those of low parity. Again, maternal morbidity is not greater in sections of high parity than in sections of low parity.

The authors believe that postoperative morbidity has no effect upon the occurrence of defective scars in later pregnancy, there being no correlation between afebrile postoperative courses and good scars, or between febrile courses and defective scars.

One fifth of all uteri removed for defective scar were judged by the pathologist, to be normal uteri; 2.1 per cent of the patients were diagnosed as having uterine rupture, and 2.6 per cent as having dehiscence. Fifteen of the 16 patients with uterine rupture underwent hysterectomy, while only one third of those with dehiscence underwent hysterectomy.

A strong argument is thus presented against routine sterilization following the third cesarean section. *Carl J. Pauerstein*

Haynes and Clemmons: Cesarean Section, p. 369.

During the 6 year period 1954 to 1959, 16,593 patients were delivered at Louisville General Hospital. Of these, 343 patients underwent cesarean section, an incidence of 2 per cent.

The major indication for cesarean section was previous cesarean section, this being the indication in 45.8 per cent of cases. Some patients with previous cesarean section were allowed to deliver vaginally. Some 22.7 per cent of the cesarean sections were performed because of "cephalopelvic disproportion." This indication was present in 41.9 per cent of the *primary* cesarean sections. All but 2 of these 78 patients were allowed a trial of labor prior to section. The remainder of indications were placenta previa (11.1 per cent), transverse presentation, prolapse of umbilical cord and abruptio placentae, and miscellaneous indications.

Twenty of the 343 cases were done by the classical technique, an incidence of 5.8 per cent.

In 9 cases it became necessary to extend a transverse lower segment incision vertically, thereby forming a T-shaped incision. In 6 of these cases a transverse presentation was present.

The predominant type of anesthesia was spinal. Inhalation anesthesia apparently was used when contraindications to spinal anesthesia existed.

The authors discuss the selection of patients with previous abdominal delivery as candidates for vaginal delivery.

Of 100 elective cesarean sections, 98 babies were term size, so that most of the cases of prematurity at cesarean section were due to emergency section. *Carl J. Pauerstein*

Chatham: Ten Year Experience With Cesarean Section in a 50 Bed Hospital, p. 374.

Experience with 72 cesarean sections, about half of which were performed by the author, is pre-

sented. The cesarean section rate was 2.5 per cent. During the years 1949 to 1958 no maternal deaths occurred and there were only 2 fetal deaths. The author does discuss a maternal death which occurred in 1959.

The incidence of classical cesarean sections in all cesarean sections is 12.5 per cent. The author states that the classical section is used "in the presence of placenta previa, and when fast action is indicated, as in abruption of the placenta or in fetal distress."

No general anesthesia was employed, all procedures being performed under local or spinal anesthesia.

All patients with previous cesarean section underwent repeat cesarean section, as the time lag required for setup for emergency operation is about one hour, and it is felt that this represents an untoward risk in the event of rupture of the uterine scar during trial labor.

Carl J. Pauerstein

Surgery, Gynecology and Obstetrics

Vol. 112, No. 5, May, 1961.

Talbert, James L., Riley, Lee H., Jr., Sabiston, David C., Jr., and Blalock, Alfred: An Evaluation of Gaseous Oxygen Perfusion as a Method for Maintaining Renal Viability During Periods of Complete Ischemia, p. 593.

Weiner Klinische Wochenschrift

Vol. 73, Jan. 20, 1961.

*Huber, A.: Vaginal Examination During Labor, p. 48.

Huber: Vaginal Examination During Labor, p. 48.

Approximately 80 per cent of 3,342 women delivered in the Hospital of the Imperial Guard of Addis Ababa were followed by vaginal examination. There resulted a 2.5 per cent morbidity during the puerperium. The author quotes figures of 2.7 per cent and 2.8 per cent following rectal and external examination respectively. Operative delivery, perineal lacerations, and other usual traumatic sequelae of delivery had no unfavorable influence on the incidence of patients with an afebrile peurperium. In spite of relatively primitive working conditions, the puerperal morbidity was not significantly higher in this series than in better staffed and housed facilities.

Douglas M. Haynes

Zentralblatt für Gynäkologie

Vol. 82, No. 37, Sept. 10, 1960.

Thomas, J.: Present Knowledge of Etiology and Incidence of Human Malformations, p. 1417.

*Sternbeck, D.: The Position of the Vacuum Extractor in Operative Obstetrics, p. 1427.

Bonivart, A., and Kneiszl, F.: Spontaneous Delivery With Central Placenta Previa—Case Report, p. 1433.

Bastian, M., and Imig, R.: Simultaneous Prolapse of Arm and Feet in Vertex Presentation at Term—Case Report, p. 1436.

Glimm, G.: Contribution on Problems of Spontaneous Rupture of the Uterus—3 Cases, p. 1440.

Sternbeck: Position of the Vacuum Extractor in Operative Obstetrics, p. 1427.

In 2 years, the vacuum extractor has been used in 153 deliveries out of a total of 4,098 (3.45 per cent). No complications are reported for mother or baby, except for accentuated caput formation. The indications were uterine inertia (49 per cent), fetal distress (15 per cent), medical complications (12 per cent), toxemia (11 per cent), malpresentation (7 per cent), and "relative disproportion" (6 per cent). There was a concurrent 50 per cent drop in frequency of forceps deliveries. The author makes the following points for this procedure: (1) safest obstetrical operation; (2) possible complete replacement of low forceps; (3) possible replacement of mid- and high- *(sic)* forceps, if there is no emergency (i.e., delivery to be accomplished in less than 10 minutes); (4) greater safety than oxytocics in inertia.

However, he also states that vacuum extraction cannot replace forceps in all cases and that thorough familiarity with mechanisms of labor and forceps is a prerequisite to acquisition of expertness in this operation. Except when used as a substitute for low forceps, the vacuum extractor should be used with intermittent pull, synchronous with contractions.

Walter F. Tauber

Items

American Board of Obstetrics and Gynecology

The Part I examinations (written) of this Board will be held in various cities of the United States, Canada, and military centers outside the Continental United States on Friday, Jan. 5, 1962.

Applicants and candidates for examination in 1963, please note that the deadline date for making application is advanced to July 1, 1962.

Current Bulletins outlining present requirements may be obtained by writing to the Executive Secretary, Robert L. Faulkner, M.D., 2105 Adelbert Road, Cleveland 6, Ohio.

International Congress on Psychosomatic Obstetrics

The first International Congress on Psychosomatic Obstetrics will be held in Paris, July 8-12, 1962, under the sponsorship of the French Society of Psychosomatic Medicine and Childbirth. The program committee is interested in papers on the psychology and sociology of pregnancy, labor, and delivery. Further inquiries may be directed to Dr. Lee Buxton, Chairman, Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, Connecticut, or to Dr. F. W. Goodrich, Jr., 342 Montauk Ave., New London, Connecticut.

Conference on "The Cervix"

The meeting place of the conference on "The Cervix" sponsored by the New York Academy of Science has been changed to the Henry Hudson Hotel, New York City.

The conference will take place Dec. 7, 8, and 9, 1961. Subjects to be discussed include: fundamental considerations, physiology—relation to infertility, benign disease of the nonpregnant cervix, the cervix of pregnancy, and diagnosis, evaluation, and therapy of cervical malignancy.

Co-chairmen are Warren R. Lang, M.D., Jefferson Medical College, Philadelphia, Pennsylvania, and Alfred B. Kupferberg, Ph.D., Ortho Research Foundation, Raritan, New Jersey.

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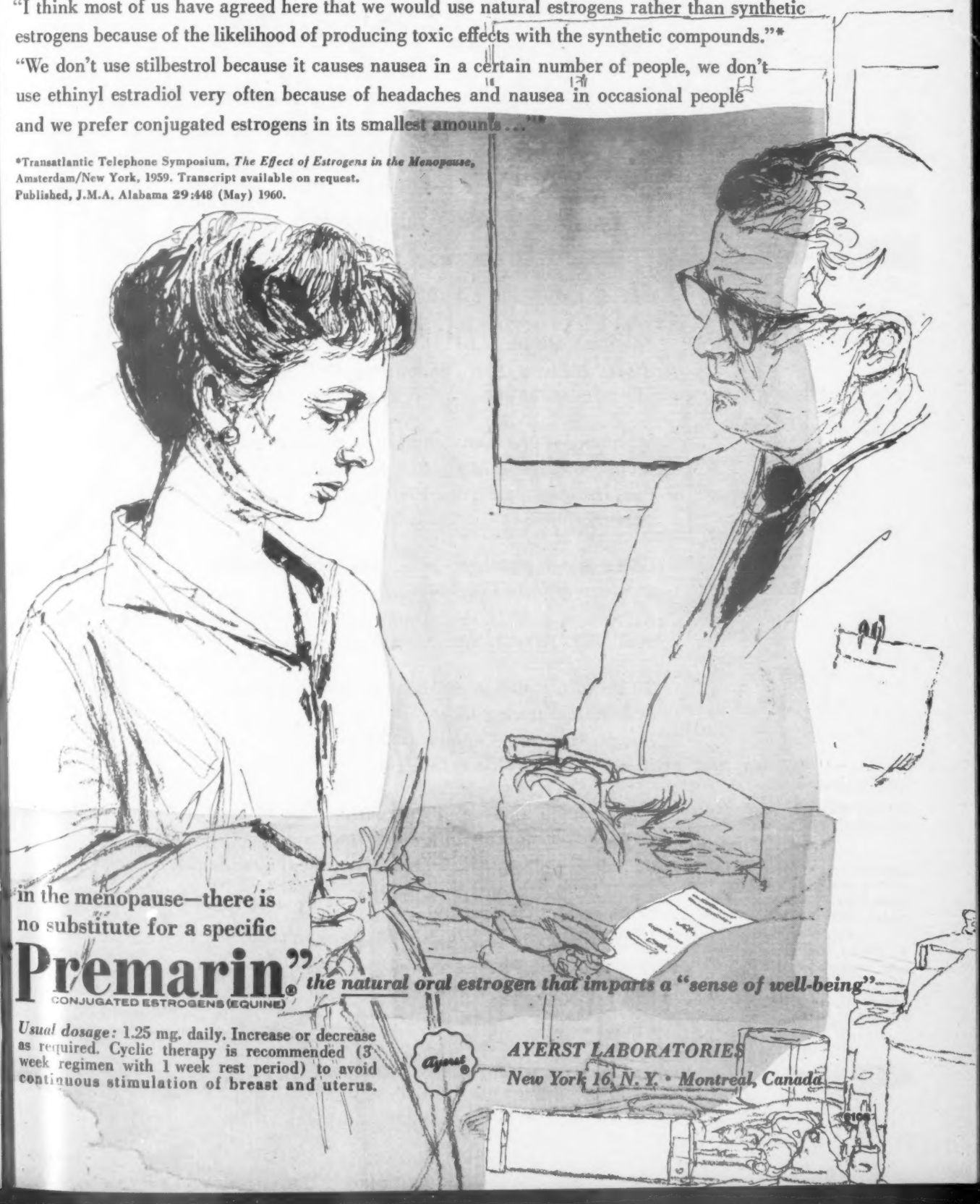
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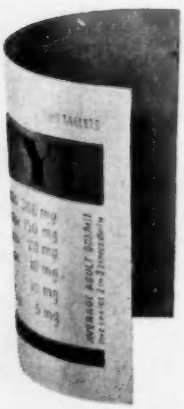
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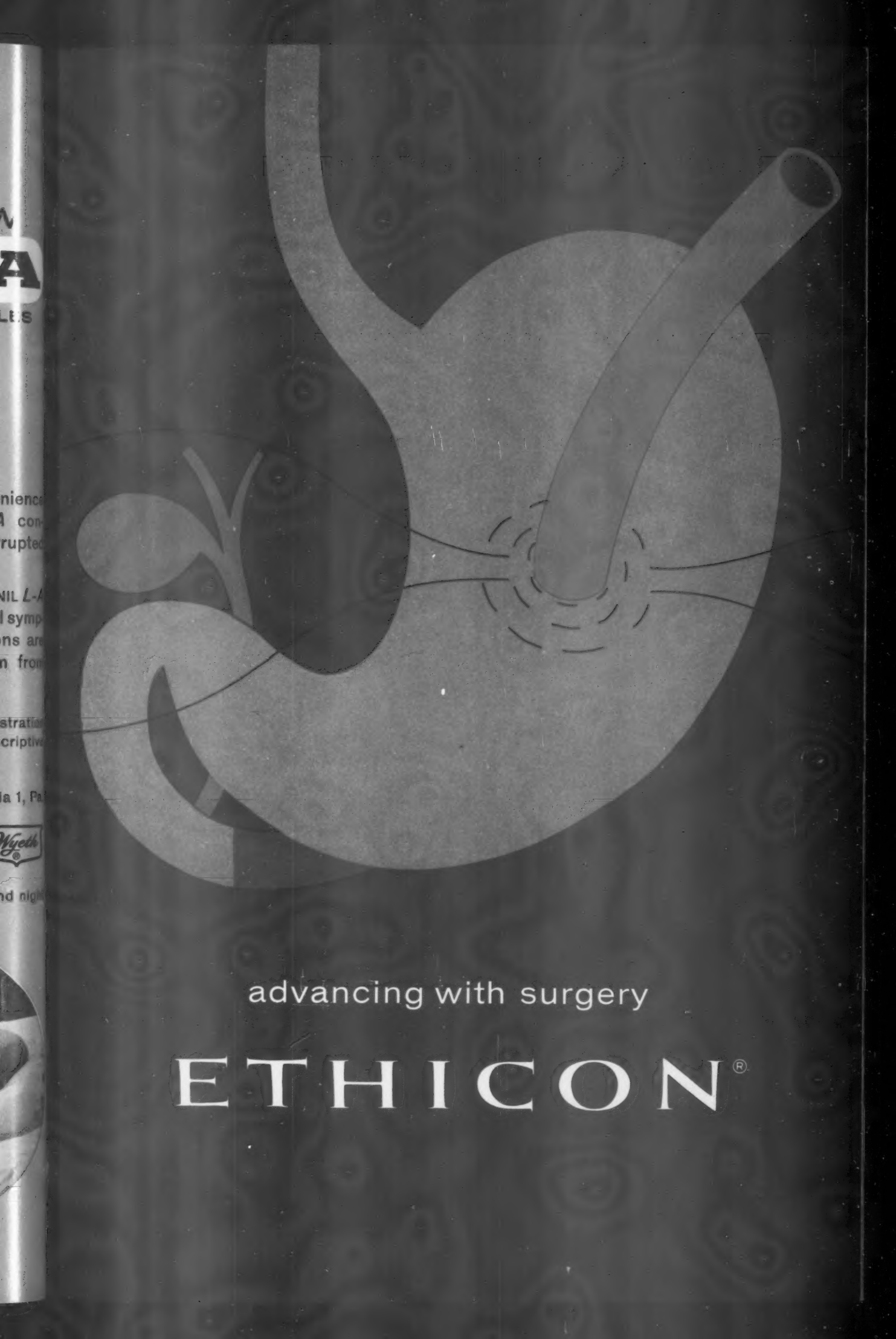
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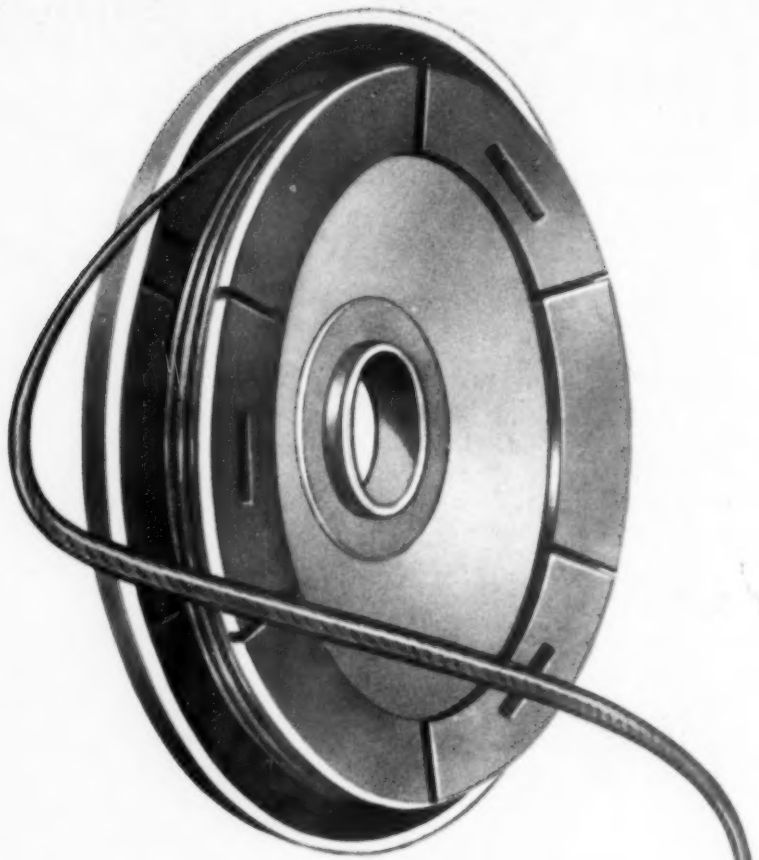
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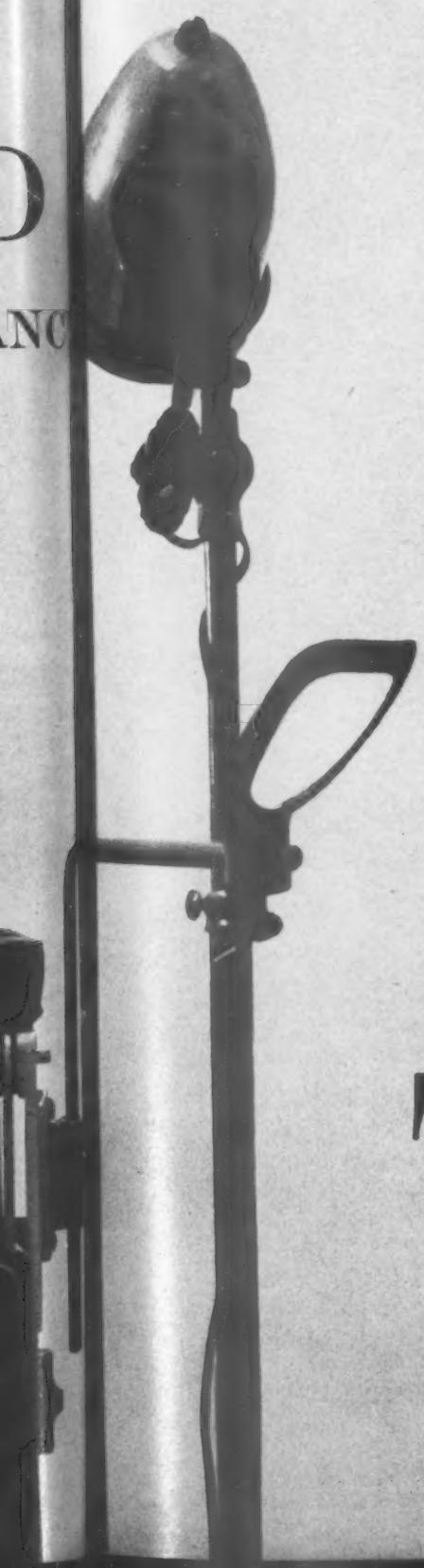
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for fetal salvage with no androgenic effect

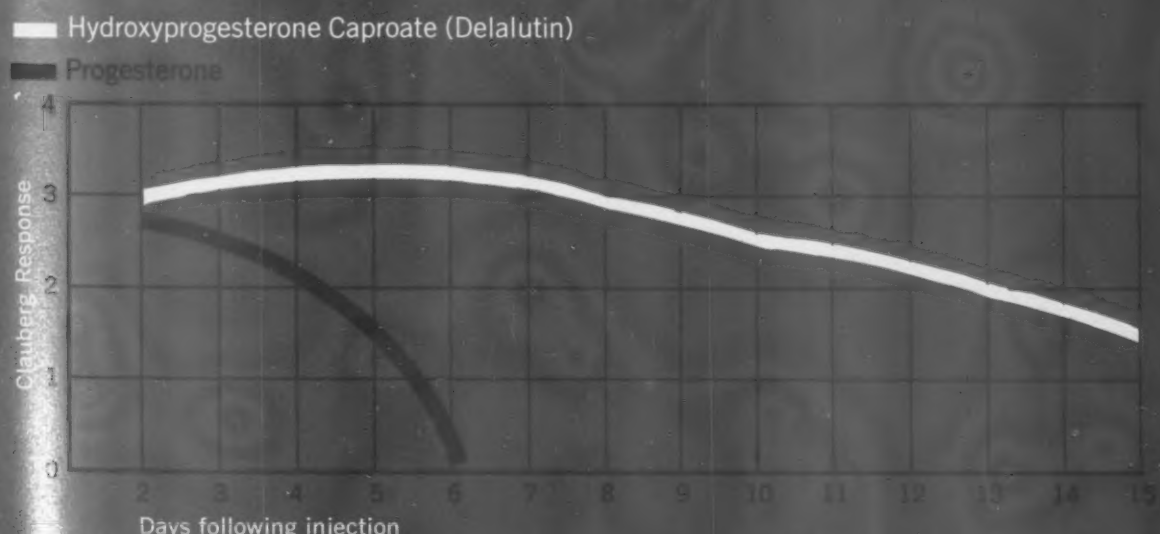
DELALUTIN®

Squibb Hydroxyprogesterone Caproate — Long-acting Progestational Therapy

Delalutin offers these advantages over other progestational agents: Significantly improved rate of fetal salvage[1-3] ■ No virilizing effect on female fetus or mother ■ High, sustained hormonal level in the uterine muscle and mucosa[4] — high enough even to replace an excised corpus luteum[5] ■ Absence of local tissue reactions[3].

Comparative effect of single subcutaneous injection of Delalutin and progesterone on the progestational changes (Clauberg Test) in the rabbit uterus.

Borman, A.: Laboratory Report on the Duration of Action of 17-Alpha-Hydroxy-progesterone-n-Caproate (Delalutin). The Squibb Institute for Medical Research, May 27, 1955.



Squibb Quality—the Priceless Ingredient


me? use vinegar?

my doctor recommends Massengill Powder!

Patients like Massengill Powder. *Its clean, refreshing fragrance and convenience are acceptable to the most fastidious.*

Massengill Powder offers other sound advantages. Massengill Powder *is buffered to maintain a pH of 3 to 4.5 for 4 to 6 hours in ambulant patients . . . 24 hours in recumbent patients.* Vinegar douches are quickly neutralized.

Massengill Powder has a low surface tension (50 dynes/cm.; vinegar is 72 dynes/cm.). *This lower surface tension means more effective penetration and cleansing of the folds of the vaginal mucosa.*

Massengill Powder is a valuable adjunct in treatment of vaginal infections. Its low pH inhibits proliferation of fungal, protozoan and bacterial pathogens but is favorable to the beneficial Döderlein bacilli.

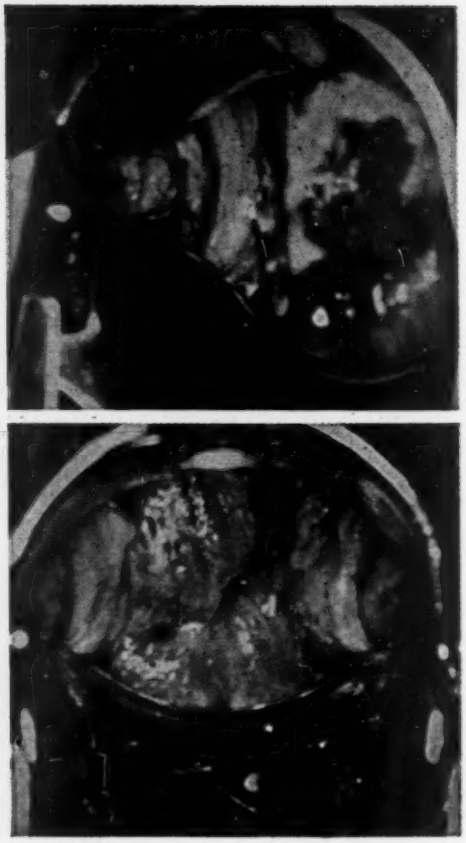
Patient cooperation is assured when Massengill Powder is recommended. Write for samples and literature.

Formula: Ammonium Alum, Boric Acid, Phenol, Eucalyptol, Berberine Salt, Menthol Isomers, Thymol and Methyl Salicylate.

MASSENGILL® POWDER

THE S. E. MASSENGILL COMPANY

Bristol, Tennessee • New York • Kansas City • San Francisco



monilial vaginitis

A COMMON PROBLEM INCREASING YEAR BY YEAR[1]

Candidiasis is especially serious in diabetics...during pregnancy...in the debilitated... and when broad spectrum antibiotics have been administered in high dosage, with or without concurrent administration of cortisone or related steroids.

Clinical Results. In 26 patients (11 pregnant) with vaginal moniliasis, treatment with Mycostatin Vaginal Tablets was completely successful in 92% of cases. Marked to moderate improvement was shown in the remainder.[2]

In a series of 59 patients with candidiasis (31 pregnant), intravaginal therapy with Mycostatin proved 100% successful in the pregnant patients; similar response was shown in 96.3% of the nonpregnant cases.[3]

Supplied: Each Mycostatin Vaginal Tablet—individually foil wrapped, contains Mycostatin, 100,000 units, and lactose, 0.93 Gm. Packages of 15 with applicator. Also available: Mycostatin Oral Tablets...Ointment...Dusting Powder...Powder for Suspension...Cream.

References: 1. Lee, A. F., and Keifer, W. S.: Northwest Med. *53*:1227 (Dec.) 1954. • 2. Caruso, L. J.: New York J. Med. *58*:1688 (May 15) 1958. • 3. Pace, H. R., and Schantz, S. I.: J.A.M.A. *162*:268 (Sept. 22) 1956.

For full information, see your Squibb Product Reference or Product Brief.

specific
highly effective
safe

Mycostatin VAGINAL TABLETS

Squibb Nystatin

SQUIBB *Squibb Quality—the Priceless Ingredient*

'MYCOSTATIN'® IS A SQUIBB TRADEMARK.

Increasingly...
the
trend is to

Terramycin®

BRAND OF OXYTETRACYCLINE

confirmed dependability in fulminating infections is just one reason why...



*New evidence** demonstrates the effectiveness of Terramycin Intravenous in appendicitis with peritonitis... another reason for the trend to Terramycin.

In a 10-year study, Wenckert and Robertson (Malmo Hospital, Sweden) found that the mortality rate in appendicitis dropped dramatically from 1.17% to 0.22% after Terramycin intravenous therapy was used routinely in those cases with associated peritonitis.

Cases of appendicitis with peritonitis found during the course of 5,564 consecutive appendectomies were treated in the first 5 years with penicillin and/or streptomycin, and those in the latter 5 years with Terramycin administered intravenously and topically. Other procedures involved in the 2 five-year series, except the different antibiotic therapies used, remained essentially the same.

The authors report: "It would, of course, have been of value if the two groups compared had dated from the same period, but in view of the favourable impression soon made by Terramycin, it was not considered justified to deprive alternate patients of the benefit of the agent [Terramycin]."

These findings confirm the life-saving, broad-spectrum dependability of Terramycin Intravenous, as reported through more than a decade of extensive clinical use in serious or fulminating infections.



In brief

The dependability of Terramycin is based on its broad range of antimicrobial effectiveness, excellent toleration, and low order of toxicity. As with other broad-spectrum antibiotics, overgrowth of nonsusceptible organisms may develop. If this occurs, discontinue the medication and institute appropriate specific therapy as indicated by susceptibility testing. Glossitis and allergic reactions to Terramycin are rare. The usual precautions required in intravenous administration should be observed. See product brochure for full information. *More detailed professional information available on request.*

another reason why the trend is to Terramycin—*versatility of dosage form:*

TERRAMYCIN Capsules
250 mg. and 125 mg. per capsule—for convenient initial or maintenance therapy in adults and older children

TERRAMYCIN Syrup / Pediatric Drops
125 mg. per tsp. and 5 mg. per drop (100 mg./cc.), respectively—deliciously fruit-flavored, preconstituted aqueous suspensions

TERRAMYCIN Intramuscular Solution
50 mg./cc. in 10 cc. vials; 100 mg. and 250 mg. in 2 cc. ampules—preconstituted, ready to use where intramuscular therapy is indicated

Terramycin®

BRAND OF OXYTETRACYCLINE

INTRAVENOUS *vials containing 250 mg. and 500 mg., buffered with 1.0 Gm., 2.0 Gm. ascorbic acid, respectively*

for most rapid and highest possible oxytetracycline blood levels / easily added to and compatible with most commonly used intravenous solutions / only 2 doses in 24 hours are necessary / well tolerated

Science for the world's well-being® Pfizer

PFIZER LABORATORIES Division, Chas. Pfizer & Co., Inc.
New York 17, N. Y.

*Wenckert, A., and Robertson, B.: Acta chir. scandinav. 120:79, 1960.

in postmenopausal vaginitis
in vaginal plastic surgery

ORTHO®

Dienestrol CREAM

vaginal estrogen therapy

builds vaginal epithelium





Naturetin releases the pent-up flood

When fluid "backs up" in the body, as it does in edematous states, Naturetin, an "...extraordinarily effective diuretic...,"[1] serves to remove fluid excess.

The diuretic effect on the patient is dramatic. Usually, the blood pressure of normotensive patients remains unaffected. Naturetin has no apparent influence of clinical importance on serum electrolytes,[2] and it causes a relatively small increase in the urinary pH.[3]

For the next patient you see with evidence of fluid retention, prescribe Naturetin and observe how the floodgates open and release the excess fluid. The average dose is a single 5 mg. tablet daily; to initiate therapy, doses up to 20 mg. may be given once daily or in divided doses.

Supply: Naturetin Tablets, 5 mg., scored, and 2.5 mg. Naturetin c K (5 c 500) Tablets, capsule-shaped, containing 5 mg. bendroflumethiazide and 500 mg. potassium chloride. Naturetin c K (2.5 c 500) Tablets, capsule-shaped, containing 2.5 mg. bendroflumethiazide and 500 mg. potassium chloride.

References: 1. David, N. A.; Porter, G. A.; and Gray, R. H.: Monographs on Therapy 5:60 (Feb.) 1960. 2. Fuchs, M.; Moyer, J. H.; and Newman, B. E.: Op. cit. 5:55 (Feb.) 1960. 3. Ford, R. V.: Current Therap. Res. 2:92 (Mar.) 1960.

For full information, see your Squibb Product Reference or Product Brief.

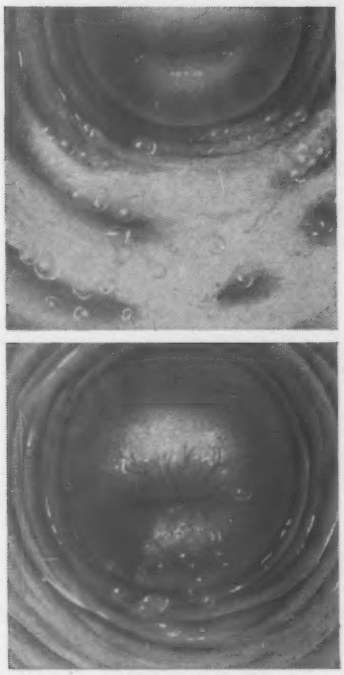
Naturetin Squibb Bendroflumethiazide

Naturetin c K Squibb Bendroflumethiazide with Potassium Chloride

SQUIBB *Squibb Quality— the Priceless Ingredient*

"NATURETIN" ® IS A SQUIBB TRADEMARK.

SQUIBB DIVISION Olin MW



in cervicitis and vaginitis

AVC

Cream & Suppositories

stops the torment destroys the cause

Action and Uses: Specific against trichomonads and highly effective in moniliasis, and nonspecific infections. Also for cervicitis and post-cauterization wounds of the cervix. **Cream:** tubes of 4 oz. with or without applicator. Each tube contains: 9-aminoacridine hydrochloride 0.2%, sulfanilamide 15.0%, allantoin 2.0%, with lactose in a water-miscible base buffered with lactic acid to pH 4.5. **Suppositories:** box of 12 with applicator. Each AVC Suppository is equivalent to one applicatorful of AVC Improved Cream. **Dosage:** one applicatorful of AVC Improved Cream or one AVC Suppository intravaginally twice daily.

DIVISION OF RICHARDSON-MERRELL INC.

AVC-745/61 P/61 THE NATIONAL DRUG CO., PHILADELPHIA 44, PA. TRADEMARK: AVC



no longer
detoured
by
diarrhea

DONNAGEL®

Donnatal® with Kaolin and Pectin compound

Robins

DONNAGEL's comprehensive antidiarrheal formulation gives the green light to normal activity, through its fast and dependable control of intestinal hypermotility.

Each 30 cc. (1 fl. oz.) of DONNAGEL contains:

Kaolin	6.0 Gm.	Natural belladonna alkaloids:	
Pectin	142.8 mg.	hyoscyamine sulfate	0.1037 mg.
Phenobarbital (¼ gr.)	16.2 mg.	atropine sulfate	0.0194 mg.
		hyoscine hydrobromide	0.0065 mg.

also available

DONNAGEL WITH NEOMYCIN • DONNAGEL-PG

DONNAGEL plus neomycin sulfate 300 mg. (as neomycin base 210 mg.) per 30 cc.

DONNAGEL plus powdered opium U.S.P. 24.0 mg. per fl. oz. (equivalent to paregoric 6 ml). This is the usual adult dose.

All three forms available in bottles of 6 fl. oz.

Menopausal distress: a syndrome involving all three levels of the autonomic nervous system

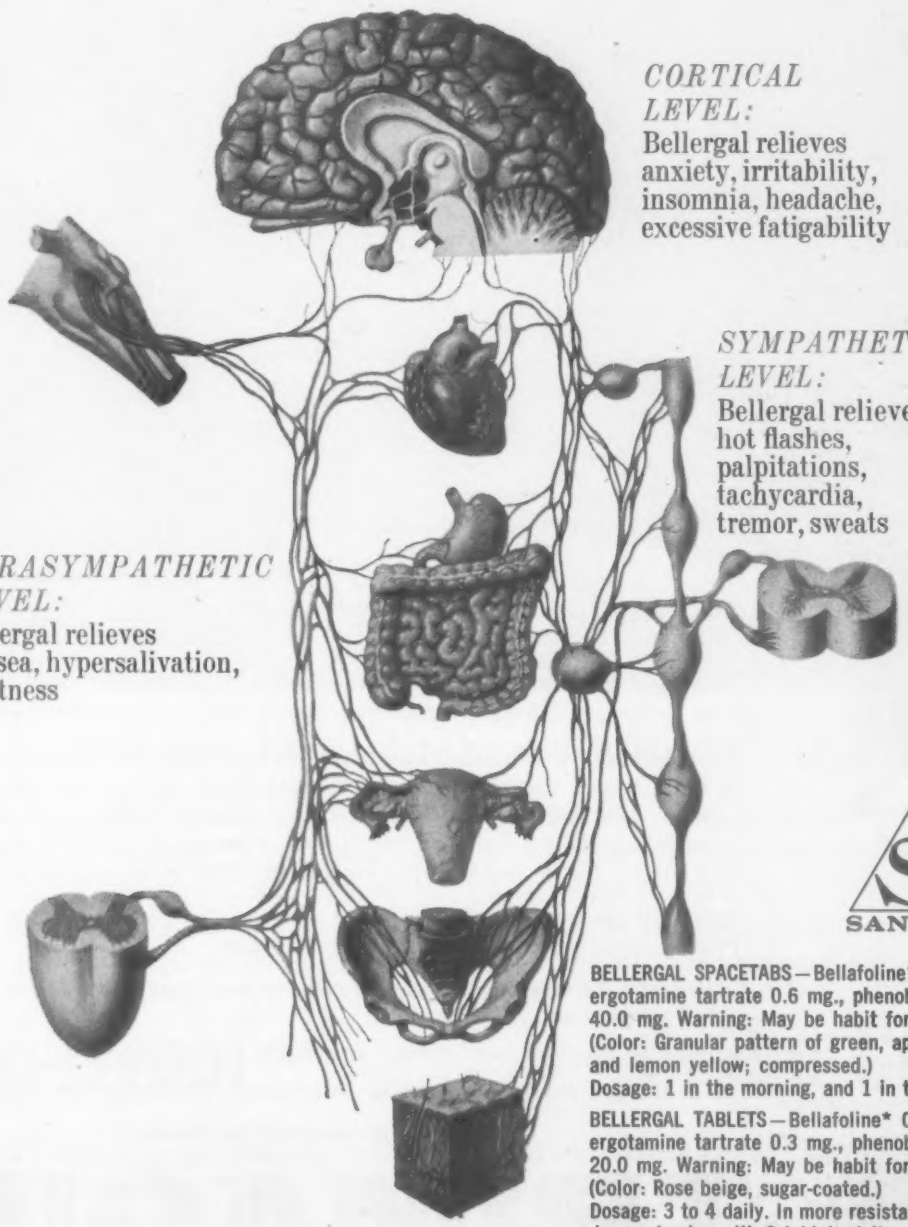
for functional disorders of the menopause

Bellergal®

SPACETABS®

stabilizes the entire autonomic nervous system

(*without disturbing endocrine balance*)



CORTICAL LEVEL:
Bellergal relieves anxiety, irritability, insomnia, headache, excessive fatigability

SYMPATHETIC LEVEL:
Bellergal relieves hot flashes, palpitations, tachycardia, tremor, sweats

PARASYMPATHETIC LEVEL:
Bellergal relieves nausea, hypersalivation, faintness

SANDOZ

BELLERGAL SPACETABS—Bellafoline* 0.2 mg., ergotamine tartrate 0.6 mg., phenobarbital 40.0 mg. Warning: May be habit forming. (Color: Granular pattern of green, apricot and lemon yellow; compressed.)
Dosage: 1 in the morning, and 1 in the evening.

BELLERGAL TABLETS—Bellafoline* 0.1 mg., ergotamine tartrate 0.3 mg., phenobarbital 20.0 mg. Warning: May be habit forming. (Color: Rose beige, sugar-coated.)
Dosage: 3 to 4 daily. In more resistant cases, dosage begins with 6 tablets daily and is slowly reduced.

*LEVOROTATORY ALKALOIDS OF BELLADONNA, AS MALATES.

Hostile Environment...



The fungus, protozoa and bacteria that commonly cause mild and severe leukorrhea require a vaginal pH of 5 to 12 for proliferation.

Trimagill creates a hostile environment! It produces a pH of 2.0 to 2.5—*the three principal infecting organisms cannot live in this acid range.*

Trimagill is well tolerated and has been proved effective in thousands of cases of leukorrhea, vaginitis, cervicitis, moniliasis and mixed infections. No untoward reactions that would require discontinuation of treatment were reported. At times denuded mucous membranes are so irritated that Trimagill may give a *temporary* burning sensation. This is usually short lived.

Trimagill does not foster resistant mutants or result in monilia overgrowth. Trimagill may be used during menstruation.

CONTENTS: Tartaric Acid, Citric Acid, Boric Acid, Dextrose, Potassium Alum, Potassium Bitartrate and Adhesives.

SUPPLIED: Powder: 5-oz. Plastic Insufflator Bottles; Vaginal Inserts: Boxes of 24

NOTE: Consult package circular for information on dosage and instructions for use.

Write for descriptive literature.

TRIMAGILL®

POWDER • VAGINAL INSERTS

THE S. E. MASSENGILL COMPANY

Bristol, Tennessee • New York • Kansas City • San Francisco

*Patent applied for.



...does she know that only **you** can help?

Many patients are unaware that their physician is the best source of contraceptive advice. Your prescription for Ortho-Gynol or Ortho-Creme with a diaphragm assures her the best available contraceptive protection. Accurate tests* for spermicidal potency, as well as years of clinical use, demonstrate that ORTHO contraceptive products are instantaneously spermicidal. The choice between Ortho-Gynol and Ortho-Creme is one of individual esthetic preference.

Ortho-Gynol®
vaginal jelly

Ortho®-Creme
vaginal cream

*The spermicidal potency of all ORTHO products is controlled by the **Titration Test** and the **Sander-Cramer Test,** which more closely duplicate vaginal conditions during coitus than other tests.

WHENEVER A DIAPHRAGM IS INDICATED

Ortho

two new important instruments for collecting uterine cytology specimens . . . in your office

NEW ADAMS ENDOMETRIAL BRUSH Pat. . . . for fast convenient collection of cytology specimens from the uterine cavity and other body orifices . . . in the physician's office. Can be directed at a specific cell site or rotated to cover a wider surface. Retractable brush design facilitates insertion . . . keeps specimens isolated from other cells. During insertion, brush is retracted inside cannula. After cannula is introduced beyond cervical os, brush is extended, rotated to collect specimens, retracted into cannula, and entire unit withdrawn. Brush bristles have flagged ends to ensure rich cell collection. The 10⅛ inch polyethylene cannula is small in diameter, soft and flexible to minimize patient discomfort. Disposable, the Endometrial Brush is packed sterile ready for use.

NEW SPECIAL AYRE CYTO-SCRAPER T.M. Pat. . . . for maximum cell collection from endocervix and enlarged (pregnant) or eroded cervix. For endocervical specimens, elongated finger end reaches into cervical os, scrapes endocervical canal as well as squamo-columnar junction. For eroded or enlarged cervices, one tip of broad end is inserted into cervical os. When rotated, cells are collected from entire circumference of squamo-columnar junctional circle. Performed in physician's office, entire procedure takes only minutes.



OTHER IMPORTANT CLAY-ADAMS CYTOLOGY SUPPLIES / *Cary Metal Uterine Cannula* / *Mass Screening Kits (packaged to specifications)* / *Papanicolaou Stains* / *Nolan-Budd Cervical Biopsy Curet* / *Medichromes®—full color 2" X2" (35mm) Kodachromes on Uterine Cytology — further information write Clay-Adams*

Available from your dealer Clay-Adams *New York 10, N. Y.*

General Use:



The general practitioner, the internist, and the surgeon alike are frequently called on to relieve pain or perform minor surgical procedures that may be successfully managed with the aid of this versatile anesthetic. Consistently effective anesthesia may be expected from Xylocaine because of its fast and profound action and its spreading ability. It is virtually nonirritating to tissues and is relatively nonsensitizing, and possesses a wide margin of safety. For topical anesthesia Xylocaine may be applied as a spray, with cotton swabs, or by packs, as well as by instillation into a cavity and application onto a surface. Local anesthesia of nerves, plexuses or terminal nerve endings requires individualized volumes and concentrations of Xylocaine, with or without epinephrine. For general use Xylocaine is recommended in concentrations of 0.5%, 1% and 2%, with the 2% solution generally used for nerve block. Minimal volumes of 4% Xylocaine may be used topically in those cases where lower concentrations are ineffective or inadequate. The 4% solution may also be used transtracheally, for retrobulbar injection, and for otological surgery, where small volumes are indicated.

Indications for topical application: Lacerations, abrasions, burns, corneal analgesia, indirect laryngoscopy, pruritus. Indications for injectable anesthesia: suturing, wound closure, causalgia, minor surgery, removal of moles, warts, and cysts, fracture reduction, bursitis, post-traumatic syndrome, herpes zoster.

Xylocaine

INJECTABLE AND TOPICAL ANESTHETIC

Surgery:



Xylocaine is well suited for infiltration and nerve block techniques for a large number of major and minor operative procedures. Xylocaine gives anesthesia of adequate duration, is fast acting with high diffusibility, and its action is predictable. Minimal dosage consistently produces profound anesthesia. The margin of clinical safety is wide, and side effects, considering the extensive use of Xylocaine, are rare. For infiltration, 0.25% and 0.5% solutions are used in volumes of 30 cc. to 100 cc. The 1% solution may be used when smaller volumes of 10 cc. to 30 cc. are to be administered. When a single injection of Xylocaine is used for peridural, spinal and other major nerve blocks, the concentration and volume varies with the type of block and the individual requirements. The total dosage of Xylocaine should *not* exceed 500 mg. when administered with epinephrine, or 300 mg. without epinephrine. Xylocaine is one of the very few anesthetic agents which are effective topically as well as by injection. This is an important advantage in many surgical procedures where mucous membranes of the respiratory, upper gastrointestinal and lower genitourinary tracts, the eye and ear, and the anorectal area are involved. The 2% and 4% concentrations of Xylocaine solutions are used for topical anesthesia. Volumes are adjusted according to the requirements of the surgical procedures being undertaken.

Xylocaine

INFILTRATION, NERVE BLOCK, AND TOPICAL

Obstetrics, Gynecology, Urology:

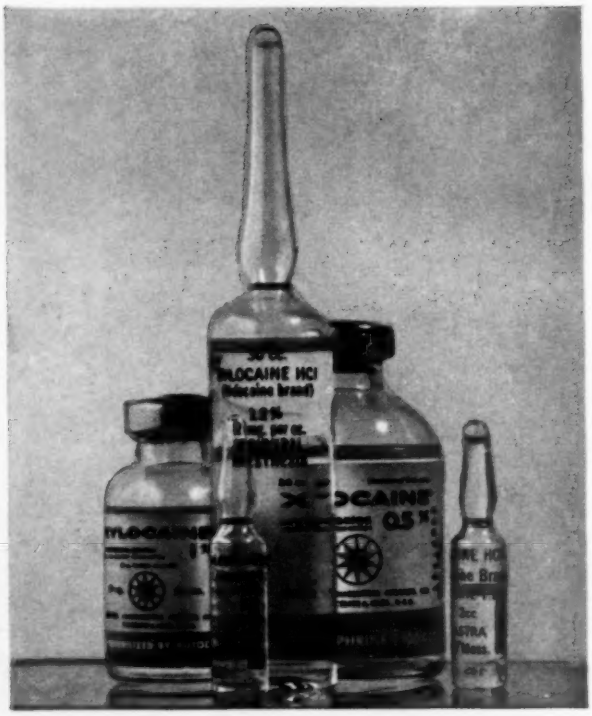


Xylocaine

PERIDURAL, CAUDAL, & SPINAL "SADDLE BLOCK"

Spotty anesthesia and slow onset, once major drawbacks of peridural and caudal techniques, occur only rarely with Xylocaine because of its high anesthetic index, wide diffusibility, short latency period, and adequate duration of nerve block. Its relative safety and reliability of performance have caused Xylocaine to be called a "...drug of choice for extradural analgesia."† Because of the wide variation in dosage required for extradural anesthesia, there are three concentrations of Xylocaine HCl available for this technique; 1%, 1.5% and 2%. All three concentrations are supplied without epinephrine or with epinephrine 1:200,000, and are dispensed in single dose containers. Operative analgesia is obtained with volumes of 25 cc to 30 cc. of 1% Xylocaine HCl. Concentrations of up to 2% are used for peridural anesthesia where complete muscular relaxation is required; this condition, however, may, in many instances, be achieved with Xylocaine HCl 1.5%. "Xylocaine spinal" may be used with predictable results for obstetrical, gynecological and urological procedures, and for surgery of the lower abdomen and the lower extremities. "Xylocaine spinal" has a low binding affinity that minimizes potential nerve injury. Its anesthetic effect is routinely rapid, profound, well tolerated and free from "spottiness." It is completely stable in the presence of spinal fluid. The anesthetic action of "Xylocaine spinal" is of moderate duration, and ranges from 100 to 140 minutes.

Xylocaine®
(brand of lidocaine*)
local anesthetic



For Infiltration and Nerve Block • Xylocaine HCl 0.5% and 1% without and with epinephrine 1:100,000 in 20 cc. and 50 cc. multiple dose vials. Xylocaine HCl 2% without and with epinephrine 1:100,000 in 20 cc. and 50 cc. multiple dose vials; also 2 cc. ampules (10's and 30's).

For Spinal Anesthesia • Xylocaine HCl 5% with glucose 7.5% (specific gravity 1.030-1.035) in 2 cc. ampules (10's and 100's).

For Peridural Anesthesia • Xylocaine HCl 1%, without epinephrine and with epinephrine 1:200,000, 30 cc.; Xylocaine HCl 1.5% without epinephrine, 20 cc.; Xylocaine HCl 1.5% with epinephrine 1:200,000, 30 cc.; Xylocaine HCl 2% without epinephrine, 10 cc.; and Xylocaine HCl 2% with epinephrine 1:200,000, 20 cc. For Continuous Peridural Anesthesia • Xylocaine HCl 1% without epinephrine, 100 cc. All Xylocaine peridural solutions are dispensed in single dose containers.

For Transtracheal Use, for Retrobulbar Injection and for Otological Surgery • Xylocaine HCl 4% without epinephrine in 5 cc. ampules (10's).

For Topical Application • Xylocaine HCl 0.5% and 1% without and with epinephrine 1:100,000 in 20 cc. and 50 cc. multiple dose vials. Xylocaine HCl 2% without and with epinephrine 1:100,000 in 20 cc. and 50 cc. multiple dose vials; also 2 cc. ampules (10's and 30's). Xylocaine HCl 4% without epinephrine in 50 cc. screw-cap bottles. (NOTE: This dispensing form is never to be used for injection.) Also available for topical use, Xylocaine Ointment 2.5% and 5%, Xylocaine Jelly 2%, and Xylocaine Viscous 2%.

Write for additional complete information concerning specific Xylocaine usage.

†*Bryce-Smith, R.: Local analgesic drugs, Brit. M.J.* 1:1039 (April 2) 1960.

Contraindications: Injection: Sepsis in region of proposed injection, severe shock and heart block. Topical: Traumatized mucosa and sepsis in the region of the proposed application.

Precautions: In general, reactions and complications are best averted by using the lowest concentration and volume of the anesthetic agent that will produce the degree of blockade desired. Injections should always be made slowly and with frequent aspiration. Infiltrations should always be made slowly and with caution. Except in those cases where vasopressor drugs are contraindicated, epinephrine should be used, in concentrations not to exceed 1:100,000, to prolong anesthesia and to reduce systemic absorption. When Xylocaine is used with epinephrine, the caution required by any vasopressor drug is in order, especially in cases of patients with hypertension, diabetes or thyrotoxicosis.

Reactions and their management: Untoward effects may occur due to unusual sensitivity, faulty technique, overdosage, and inadvertent intravascular or subarachnoid injection. The type of toxic reaction is unpredictable and depends on dosage, rate of absorption and status of the patient. Reactions due to systemic absorption are primarily of two types and referable to stimulation and/or depression of the cerebral cortex and medulla.

A. Slow onset—stimulation leading to: nervousness, dizziness, blurred vision, nausea, tremors, convulsions, hypotension, cardiovascular depression and respiratory arrest.

B. Rapid onset—depression leading primarily to respiratory arrest, cardiovascular collapse and cardiac arrest. This type of reaction calls for extreme preparedness—symptoms occur rapidly and with little warning. With prompt recognition and treatment, symptoms usually are readily controlled. Maintain a patent airway and administering oxygen assure adequate ventilation; administration of a small amount of a short-acting barbiturate or a muscle relaxant controls convulsions; vasopressors, used if indicated, support circulation.

Astra Pharmaceutical Products, Inc.
Worcester 6, Massachusetts

Printed in U.S.A. Copyright 1961 *U.S. Pat. No. 2,441,498



Natalins® tablets

comprehensive vitamin-mineral support, pre- and post-natal

Only one Natalins tablet per day provides generous amounts of iron, calcium, and vitamin C, plus 8 other important vitamins. This special formula helps assure, in multiparas, the extra nutritional protection they—particularly*—need. It naturally follows that this formulation will be adequate for the primigravida.

*Taylor, J. B., and Torpin, R.: Am. J. Obst. & Gynec. 61:71-74 (Jan.) 1951.

With their new smooth coating, Natalins tablets are easier to swallow—and they disintegrate rapidly and fully for maximum utilization.

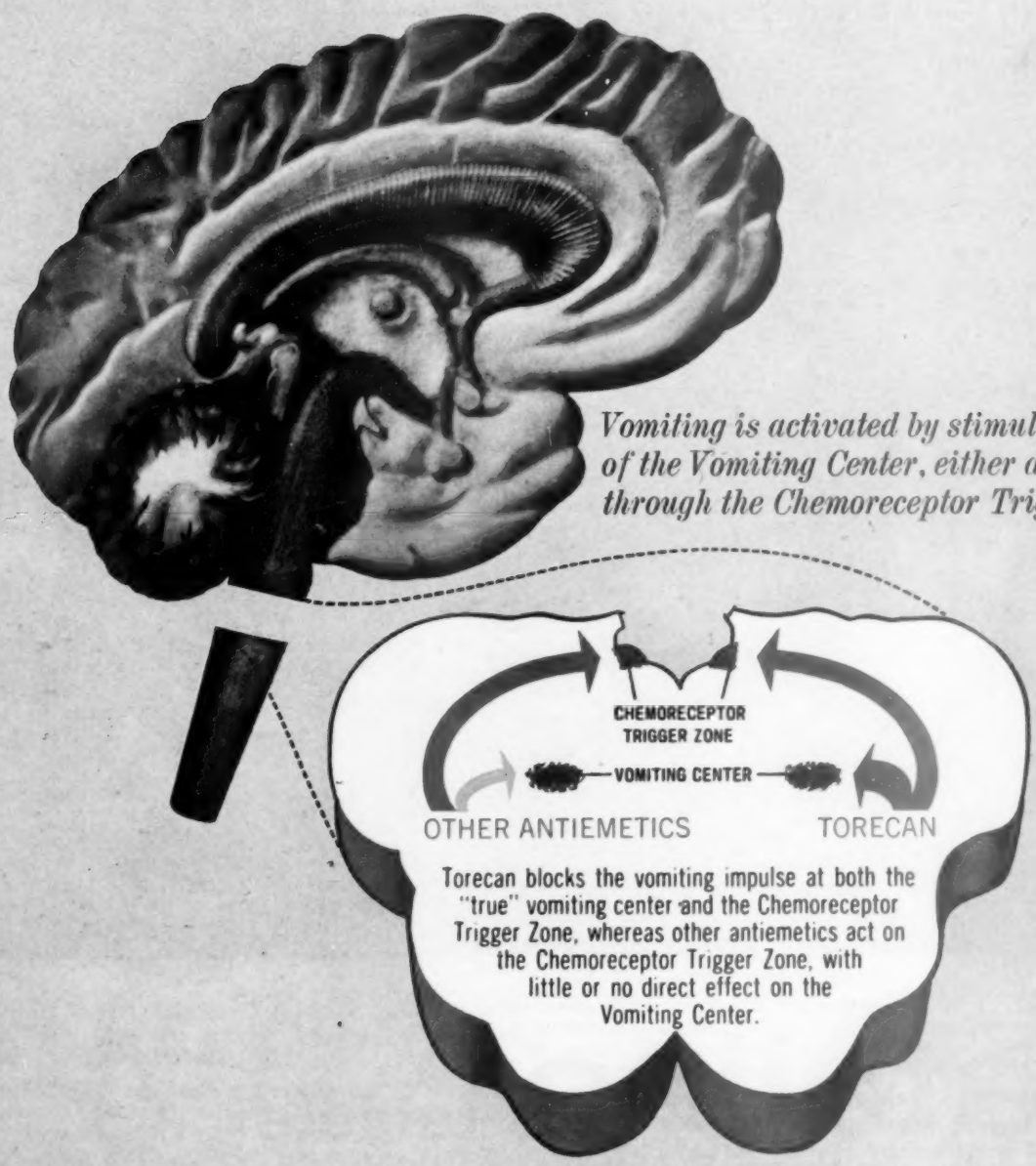
For your convenience in specification, Natalins tablets and Natalins Basic tablets have replaced all other Natalins formulations.

52461

Mead Johnson Laboratories

Symbol of service in medicine

Announcing...a "broadening of the antiemetic spectrum of effectiveness"



Vomiting is activated by stimulation of the Vomiting Center, either directly through the Chemoreceptor Trigger Z

Torecan blocks the vomiting impulse at both the "true" vomiting center and the Chemoreceptor Trigger Zone, whereas other antiemetics act on the Chemoreceptor Trigger Zone, with little or no direct effect on the Vomiting Center.

"Thiethylperazine dimaleate [TORECAN] inhibits apomorphine vomiting [apomorphine elicits vomiting solely through the Chemoreceptor Trigger Zone[2,3,4]] in an even more pronounced manner than the well-known strong antiemetic, prochlorperazine. Thiethylperazine dimaleate also antagonizes oral copper sulfate [copper sulfate may activate the Vomiting Center directly or may act via the Chemoreceptor Trigger Zone]. Interestingly, only slightly higher dosages are needed for this than for the inhibition of apomorphine vomiting, whereas far higher dosages are required of other phenothiazines. This peculiarity of thiethylperazine of influencing not only the trigger zone, but also the vomiting center is of much therapeutic interest because of the broadening of the antiemetic spectrum of effectiveness."[1]

"When evaluating new antiemetic agents, it is necessary to pay close attention to the associated effects on the central and autonomic nervous systems. The aim is to find agents which will specifically depress the emetic mechanism with minimal effects elsewhere."[5]

TORECAN

provides specific antiemetic action with minimal "spillover" effects:

Tranquilizing or sedative action	Insignificant
Potentiation of sedative and anesthetic drugs	Only slight potentiation; less than with other phenothiazine antiemetics
Extrapyramidal symptoms, such as motor restlessness, muscular rigidity, parkinsonism, etc.	Rarely at dosage levels of 30-50 mg. per day
Cardiovascular effects (hypotension, cardiac acceleration)	Rare; less than with other phenothiazine antiemetics
Liver, blood, or renal toxicity	None reported
Other side effects: dizziness, dry mouth, weakness, fatigue, blurring of vision, headache, insomnia, constipation or diarrhea	Rare

"an extremely effective antiemetic in a large number of clinical conditions"[5]

Nausea and Vomiting of Pregnancy[6]

Nausea and Vomiting Associated with Gastroenteritis and Colitis[5,6,7]

Nausea and Vomiting due to Radiation and Nitrogen Mustard Therapy[1]

Postoperative Nausea and Vomiting[5]

Nausea and Vomiting Associated with Miscellaneous Non-inflammatory Conditions[5,6,7]

Nausea and Vomiting Associated with Labyrinthine Disturbances

Adult Dosage: Oral: 1 tablet 3 times daily
Intramuscular: 10 — 20 mg. daily

Supply: Tablets, 10 mg.; Ampuls, 2 cc. (10 mg.), each cc. contains 5 mg.

Precautions: It is obvious that, before using an antiemetic, clinical judgment must be exercised in determining whether vomiting represents a warning of organic abnormality and that this must first be recognized before employing a potent antiemetic such as TORECAN. Drowsiness and/or dryness of the mouth may occur with doses above 30 mg. daily. While no hepatic, hematopoietic or renal toxicity have been reported at recommended dosage levels, it should be remembered that these reactions may occur with phenothiazines. Orthostatic hypotension may be manifested at higher dose levels. TORECAN is contraindicated in severely depressed or comatose states. In excessive doses, TORECAN may produce extrapyramidal stimulation with the varied symptom complex characteristic of this complication. Ampuls are recommended for **intramuscular injection only.**

References: 1. Codiga, V. A.: A new antiemetic for the treatment of nausea and vomiting associated with roentgen therapy, Int. Rec. Med., 174:375 (June) 1961. 2. Wang, S. C. and Borison, H. L.: The vomiting center: its destruction by radon implantation in dog medulla oblongata, Am. J. Physiol. 166:712 (1951). 3. Wang, S. C. and Borison, H. L.: A new concept of organization of the central emetic mechanism: recent studies on the sites of action of apomorphine, copper sulfate and cardiac glycosides, Gastroenterol. 22:1 (1952). 4. Wang, S. C. and Glaviano, V. V.: Locus of emetic action of morphine and hydergine in dogs, J. Pharmacol. & Exper. Therap. 111:329 (1954). 5. Browne, D. C. and Sparks, R.: Vomiting mechanisms: a clinical study of thiethylperazine, South. M.J., 54:(Sept.) 1961. 6. Browne, D. C. and Sparks, R. D.: Nausea and vomiting, study of thiethylperazine, Scientific Exhibit, American Medical Association Clinical Meeting, Washington, D.C., Nov. 28 (1960). 7. Maritano, M., Guerrieri, S., Menesini, R.: Prophylaxis and therapy of vomiting, Minerva anest. 26:343 (1960). 8. Modell, W.: Drugs of choice 1960-1961. C. V. Mosby Co., St. Louis, 1960, p. 339.

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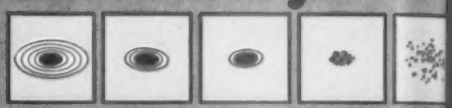
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Formula: Each special coated tablet cont
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Decapryn (doxylamine) succinate, 10 m
Pyridoxine hydrochloride, 10 mg.

References: 1. Middleton, T. F.: Postgrad. Med. 24:
1958. 2. Geiger, C. J., *et al.*: Obst. & Gynec. 5:
3. Nulsen, R. O.: Ohio State M. J. 53:665, 1957. 4. T
J. E.: Internat. Rec. Med. 171:583, 1958. 5. Woodhill, R.
Western Med. 1:13,1960. 6. Personal communications: 19

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Confirming the views of many others,[1-3] Romney[4] has recently pointed out that *Trichomonas* may be harbored asymptomatically in the male and transmitted to the female to produce a resistant vaginitis; and that "... therapy which is directed solely towards the female patient is unrealistic and ineffectual." For this reason, the husband's cooperation must be enlisted in order to end this cycle of infection and re-infection.



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1. Karnaky, K. J.: South. M. J. *51*:925 (July) 1958.
2. Giorlando, S. W., and Brandt, M. L.: Am. J. Obst. & Gynec. *76*:666 (Sept.) 1958.
3. Davis, C. H., and Grand, C. G.: Am. J. Obst. & Gynec. *68*:559 (Aug.) 1954.
4. Romney, S. L.: M. Sc. *8*:235 (Aug. 25) 1960.

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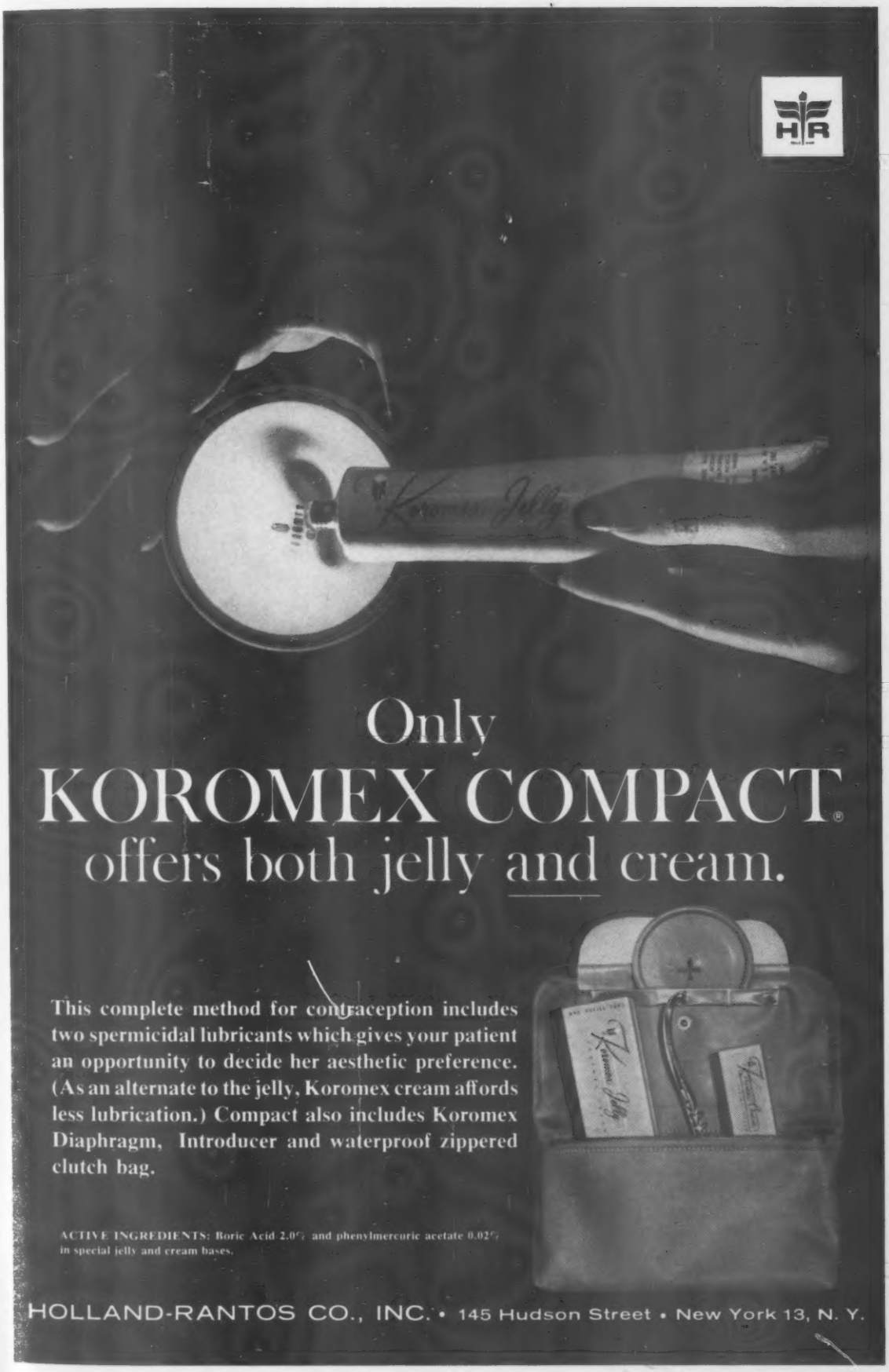


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1. N.N.R., 1959, 515; 2. Ibid., 376

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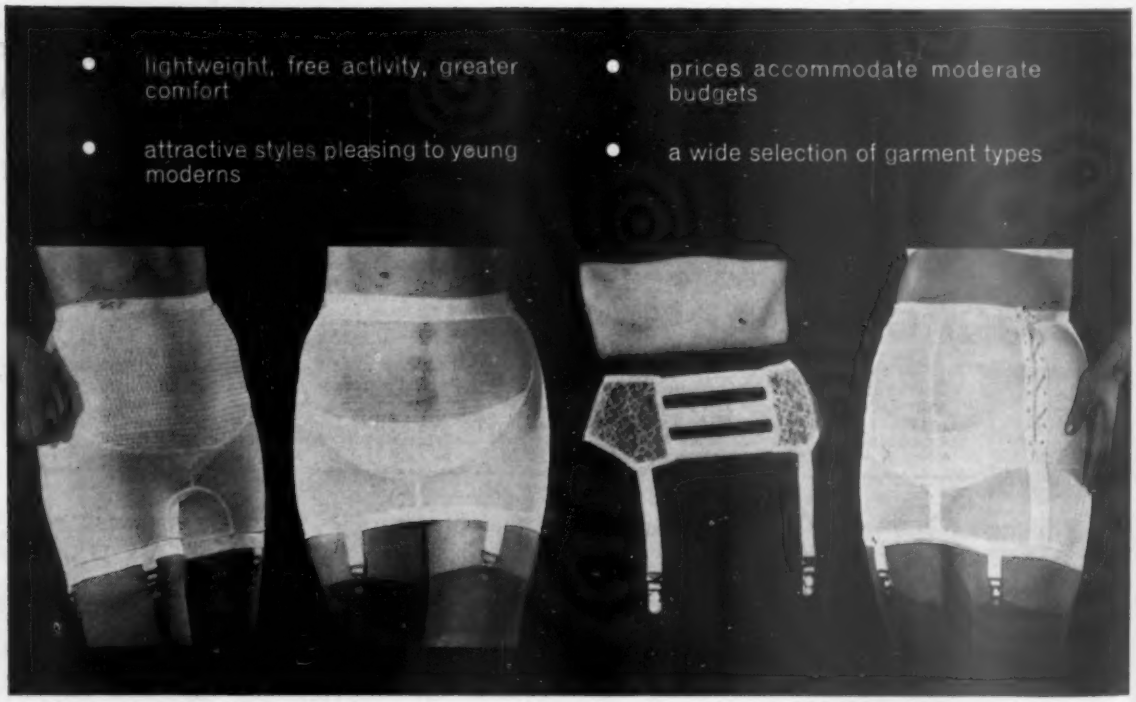
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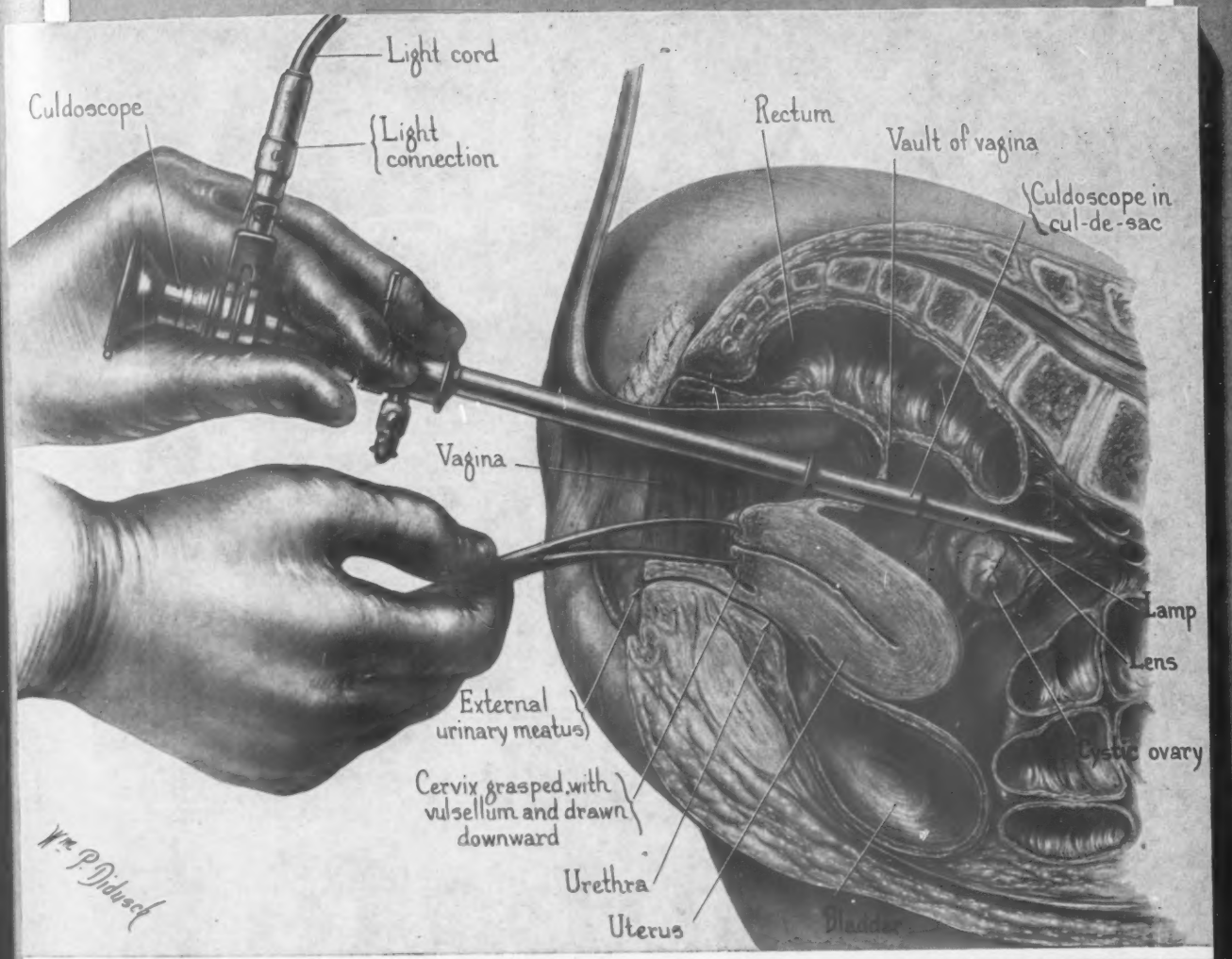
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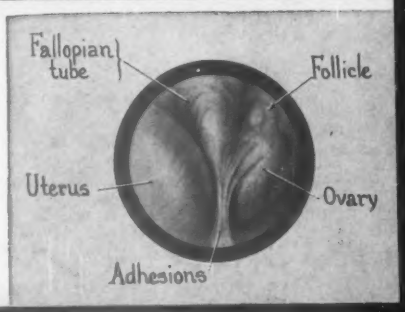
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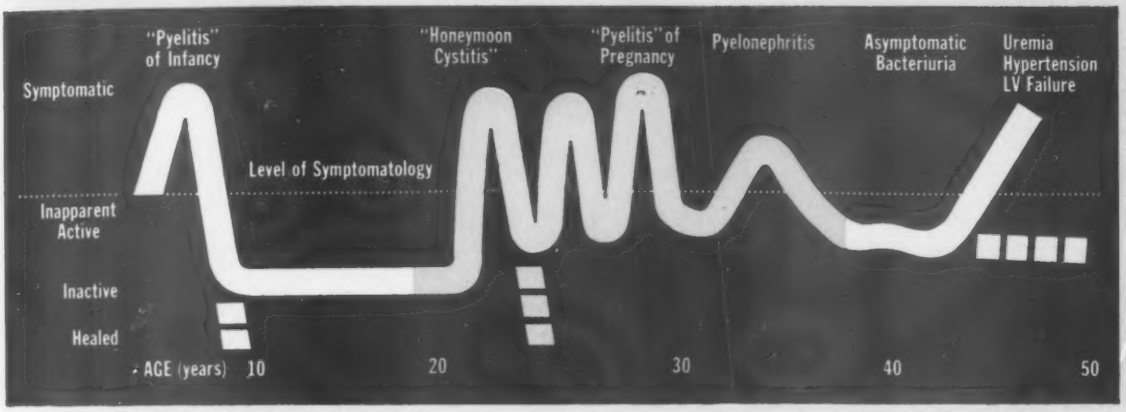
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Natural History of Pyelonephritis



". . . the theme that runs through the carefully taken history of most uremic patients with chronic pyelonephritis—the burning on urination of infancy, the chills and fever in childhood, the 'honeymoon' pyelitis, the recurrent urethritis treated so well and often locally—and yet the termination in uremia."[1]

the child-bearing age—a second major stage for urinary tract infection

"The fact that the many cases of chronic and finally, lethal, upper urinary infections in women begin or recur during gestation is especially challenging."[2] "We now believe that all prepartum women should have one quantitative urine culture as part of their medical management."[3]

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SUPPLIED: Tablets, 50 mg. and 100 mg. Oral Suspension, 25 mg. per 5 cc. tsp.

REFERENCES: 1. Birchall, R.: Am. Practit. *11*:918, 1960. 2. Benson, R. C., and Mitchell, J. C.: Clin. Obstet. Gynec. *1*:97, 1958. 3. Favour, C. B.: Southern Med. J. *54*:848, 1961. 4. Nesbitt, R. E. L., Jr., and Young, J. E.: Obstet. Gynec. (N. Y.) *10*:89, 1957.

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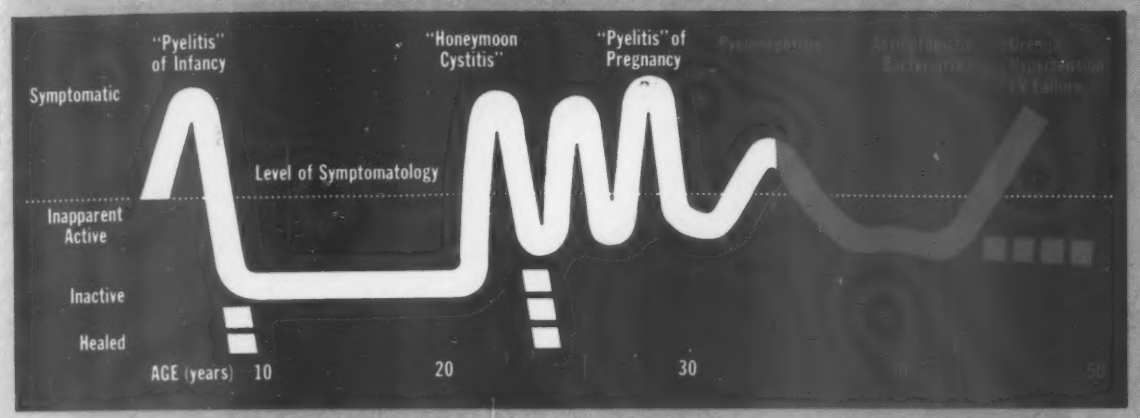
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"... the theme that runs through the carefully taken history of most uremic patients with chronic pyelonephritis—the burning on urination of infancy, the chills and fever in childhood, the 'honeymoon' pyelitis, the recurrent urethritis treated so well and often locally—and yet the termination in uremia."[1]

during the middle and later years—relapse, reinfection, renal failure

"... the physician treating a patient with established chronic urinary tract infection faces a grave problem of management."[2]

Furadantin—to preserve function; to prolong life

"... certain patients with renal insufficiency derived measurable benefit from prolonged nitrofurantoin treatment; as infection was suppressed their renal function improved. This effect was sufficiently pronounced to be considered an important component of the management of uremia accompanying chronic pyelonephritis."[2]

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SUPPLIED: Tablets, 50 mg. and 100 mg. Oral Suspension, 25 mg. per 5 cc. tsp.

REFERENCES: 1. Birchall, R.: Am. Practit. *11*:918, 1960. 2. Jawetz, E., et al.: A.M.A. Arch. Intern. Med. *100*:549, 1957. 3. Lippman, R. W., et al.: J. Urol. *80*:77, 1958.

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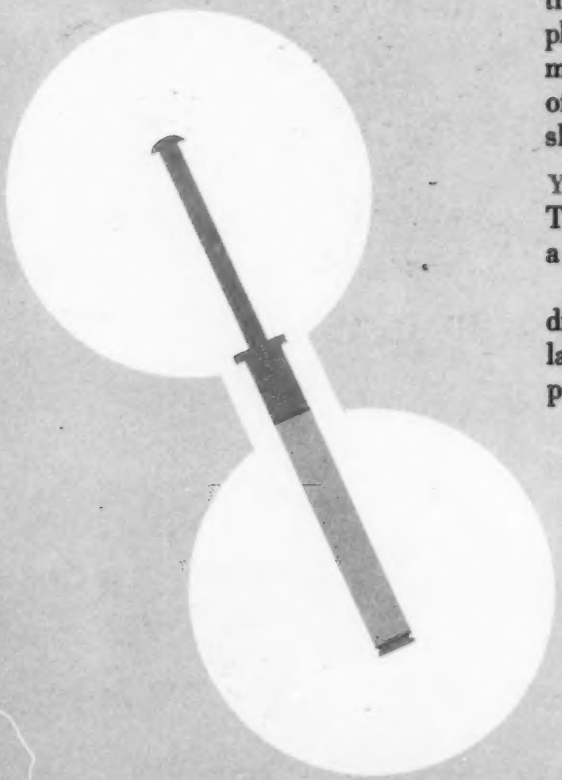
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THE CASE AGAINST CATHETERS & ENEMAS

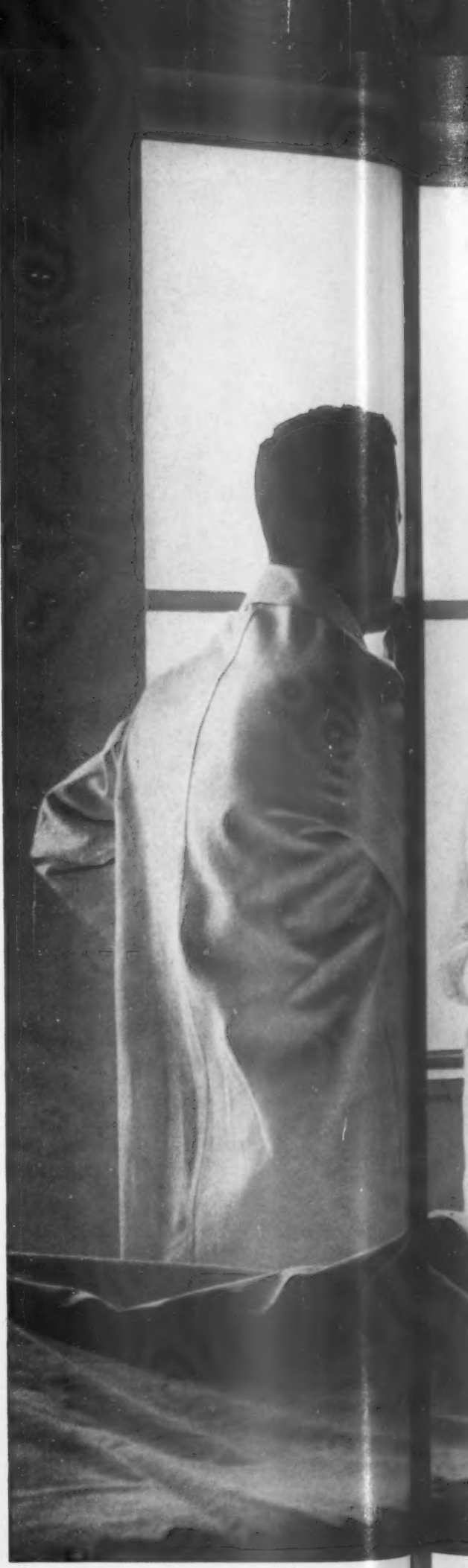


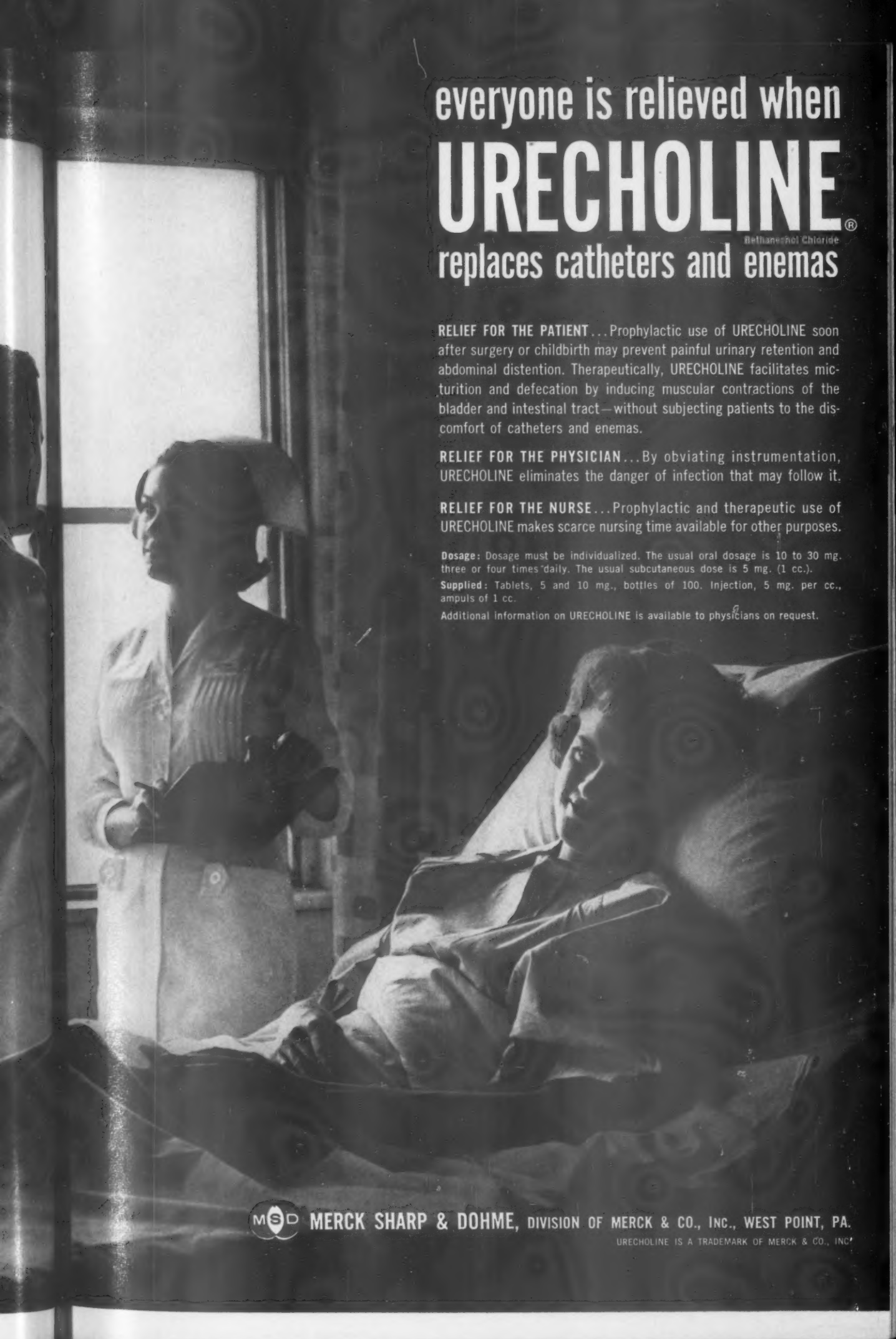
Catheters and enemas may be highly useful postoperatively and postpartum, but they are capable of serious drawbacks.

PATIENTS often dislike and fear such instrumentation, sometimes even more than the surgery or delivery that preceded it.

PHYSICIANS are mindful of the frequent risk of infection following catheterization, despite the most painstaking techniques. The passage of a sterile catheter into the bladder may introduce pathogens, since the urethra is not always sterile nor can it be readily sterilized.

NURSES find that catheterization and the administration of enemas require considerable time, which might be advantageously employed for other nursing procedures.





everyone is relieved when URECHOLINE®

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RELIEF FOR THE PATIENT... Prophylactic use of URECHOLINE soon after surgery or childbirth may prevent painful urinary retention and abdominal distention. Therapeutically, URECHOLINE facilitates micturition and defecation by inducing muscular contractions of the bladder and intestinal tract—without subjecting patients to the discomfort of catheters and enemas.

RELIEF FOR THE PHYSICIAN... By obviating instrumentation, URECHOLINE eliminates the danger of infection that may follow it.

RELIEF FOR THE NURSE... Prophylactic and therapeutic use of URECHOLINE makes scarce nursing time available for other purposes.

Dosage: Dosage must be individualized. The usual oral dosage is 10 to 30 mg. three or four times daily. The usual subcutaneous dose is 5 mg. (1 cc.).

Supplied: Tablets, 5 and 10 mg., bottles of 100. Injection, 5 mg. per cc., ampuls of 1 cc.

Additional information on URECHOLINE is available to physicians on request.

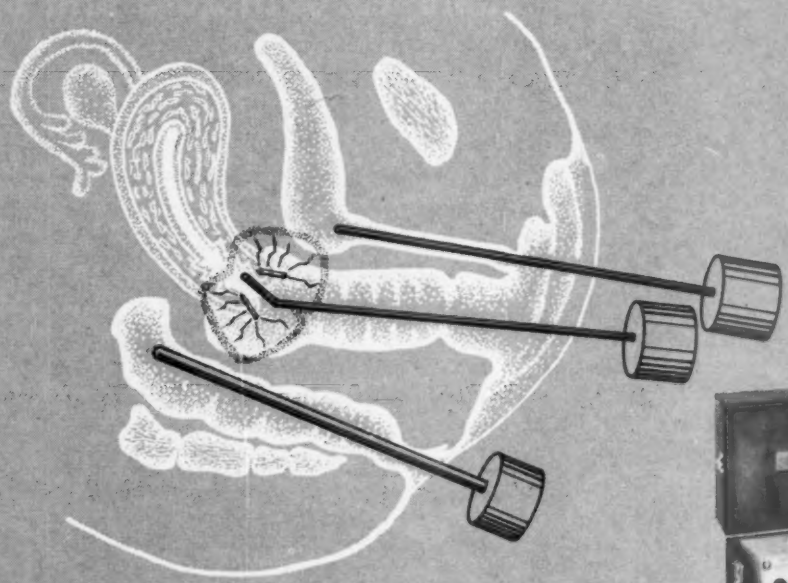
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references: 1. Myers, J.D., et al.: Scientific Exhibit, A.M.A. Clinical Meeting, Washington, D.C., Nov. 29-Dec. 2, 1960. 2. Case reports on file, Medical Department, Wyeth Laboratories. 3. Glisson, C. S., and Pratt, C.: Bull. Fulton County Med. Soc. *35*:17 (June 1) 1961.

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For further information on prescribing and administering LARGON, consult current Direction Circular enclosed with medication, or available on request.

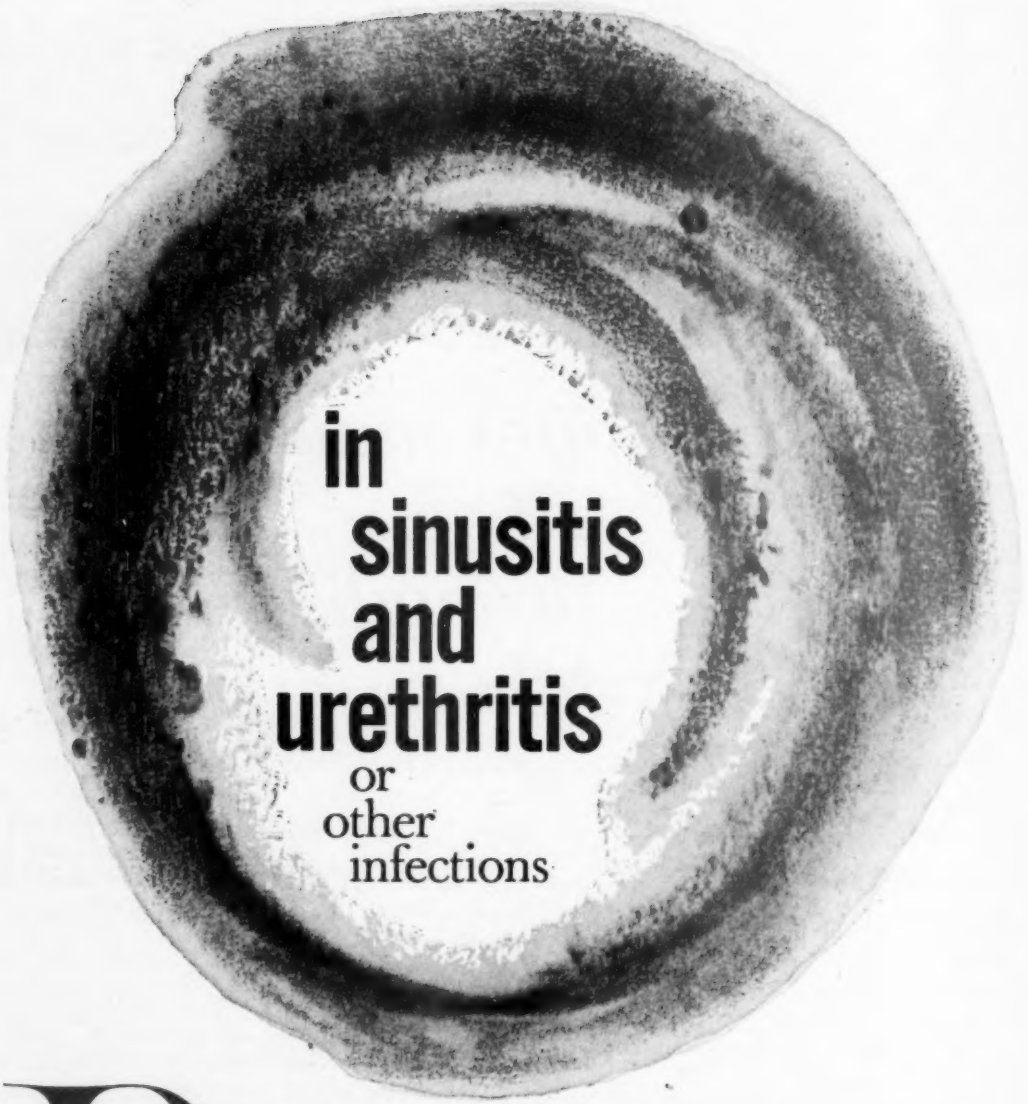
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1. Weinstein, J.J.: unpublished manuscript.

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1. Ford, R. V.: Current Therap. Res. 3:320, July, 1961

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1. Roll, W. A., and Waller, J. I.: J. Urol., Balt. 81:289, 1959.

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The extensive bibliography* on Dulcolax, amounting to almost 100 clinical reports, strongly affirms its clinical advantages.

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The Clinical Study:[1]

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The Clinical Result:

The entire group averaged a weight loss of 15 pounds between two and 12 months of treatment. Eight women, weighing between 178 and 269 pounds, took Desoxyn for six months. They averaged a loss of 34 pounds. The heaviest woman lost 57 pounds, while another lost 71 pounds.

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The clinician noted that there was an occasional finding of tablets in stools. He wrote: "A certain doubt existed in our minds that this residual tablet did not contain amphetamine. We arranged



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1. Cole, R. E., Communication to Medical Department, Abbott Laboratories, 1961.

The Drug:

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All-Day Appetite Control from a Single Oral Dose—5, 10 or 15 mg.

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then to maintain patient comfort

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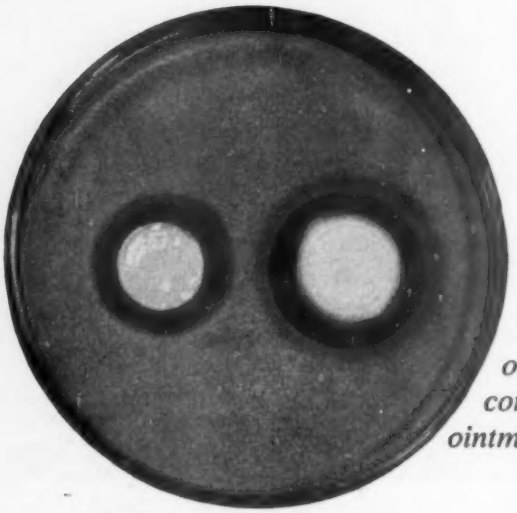
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Neither Anusol nor Anusol-HC contains analgesic or anesthetic drugs which might mask symptoms of serious rectal pathology.

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This agar plate, containing *Staph. aureus*, was incubated for 24 hours at room temperature. Note the greater zone of inhibition around Neo-Polycin Ointment (right), than around the grease-base ointment of comparable antibiotic content (left). Tests on the following pathogens gave similar results: *beta hemolytic strep., E. coli, Proteus vulgaris, Pseudomonas aeruginosa.* Higher concentrations of antibiotics released from Neo-Polycin tend to inhibit the growth of relatively resistant strains and minimize antibacterial resistance created by sub-effective concentrations.

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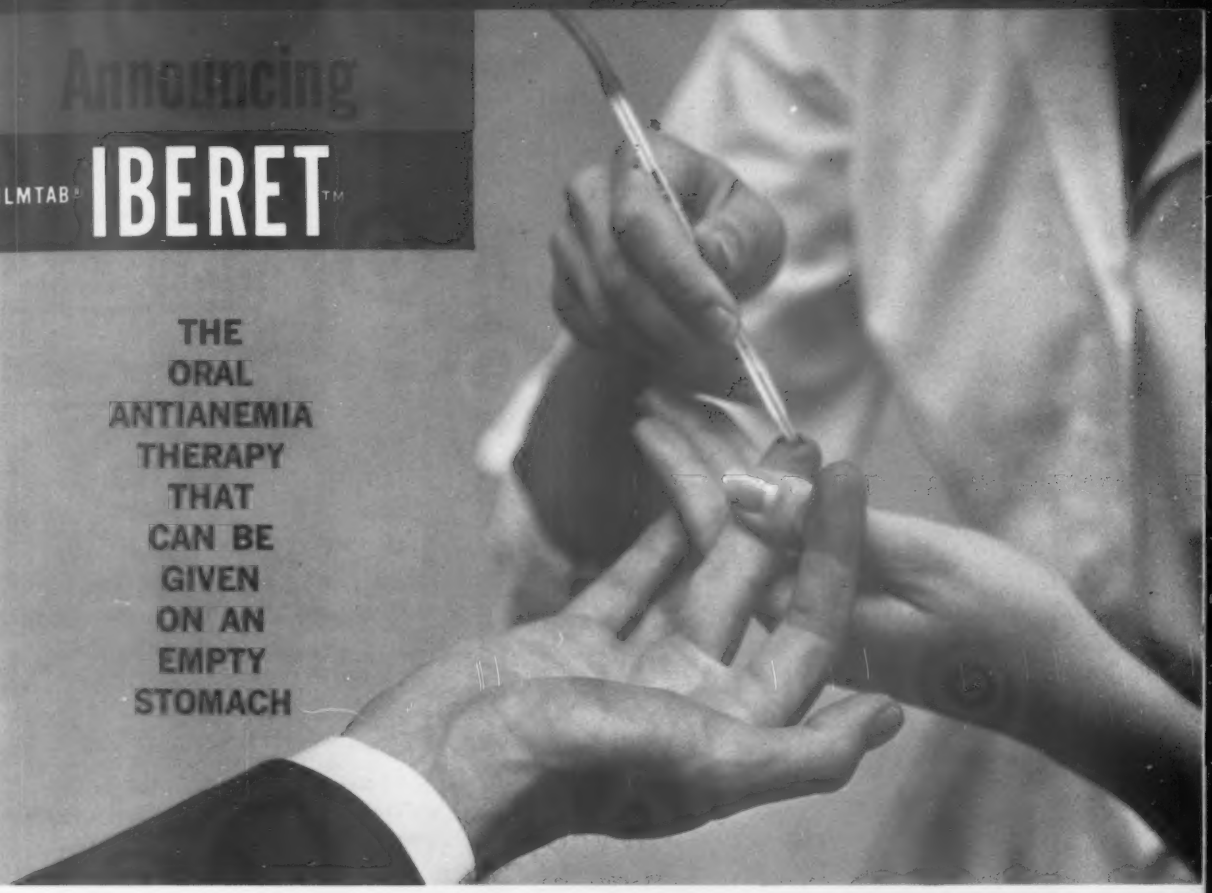
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In view of the multiple factors which can adversely affect iron absorption, it has been stated that, ". . . therapeutic iron should be given on an empty stomach."[1] But, in the past, this meant a greater incidence of side effects such as nausea, abdominal pain, diarrhea or constipation, and even heartburn.

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Cobalamin (Vitamin B_{12})	25 mcg.
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Riboflavin	6 mg.
Nicotinamide	30 mg.
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Calcium Pantothenate	10 mg.

Plus Vitamin C

Ascorbic Acid	150 mg.

Note: Filmtab® Fero-Gradumet™ with 105 mg. of Elemental Iron only, in long-release dose form, is also available.

[1]Woodruff, C.W., "Iron"; Borden's Review of Nutrition Research, 20:61, 1959.
[2]Vilter, R.W., "Essential Nutrients in the Management of Hematopoietic Disorders of Human Beings"; Am. J. Clin. Nutrition, 3-72, 1955.
[3]Brown, M.J., "Nutritional Problems in Surgery"; Surg. Clin. North America, 34-1239, 1954.

*In controlled-release dose form.
Filmtab—Film-sealed tablets, Abbott: U.S. Patent No. 2,881,085.
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Calcium Pantothenate (as Calcium Pantothenate, Racemic)	5 mg.
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brand of dimenhydrinate
For dizziness/vertigo in older patients

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*Transatlantic Telephone Symposium, *The Effect of Estrogens in the Menopause*, Amsterdam/New York, 1959. Transcript available on request.
Published, J.M.A. Alabama 29:448 (May) 1960.



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for a faster recovery with more comfort

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References: 1. Monias, M. B., et al.: Maryland State Med. J. 9:439 (Aug.) 1960. 2. Duncan, A. S.: Brit. Med. J. 1:439 (Feb. 23) 1957.

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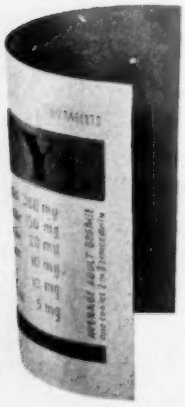
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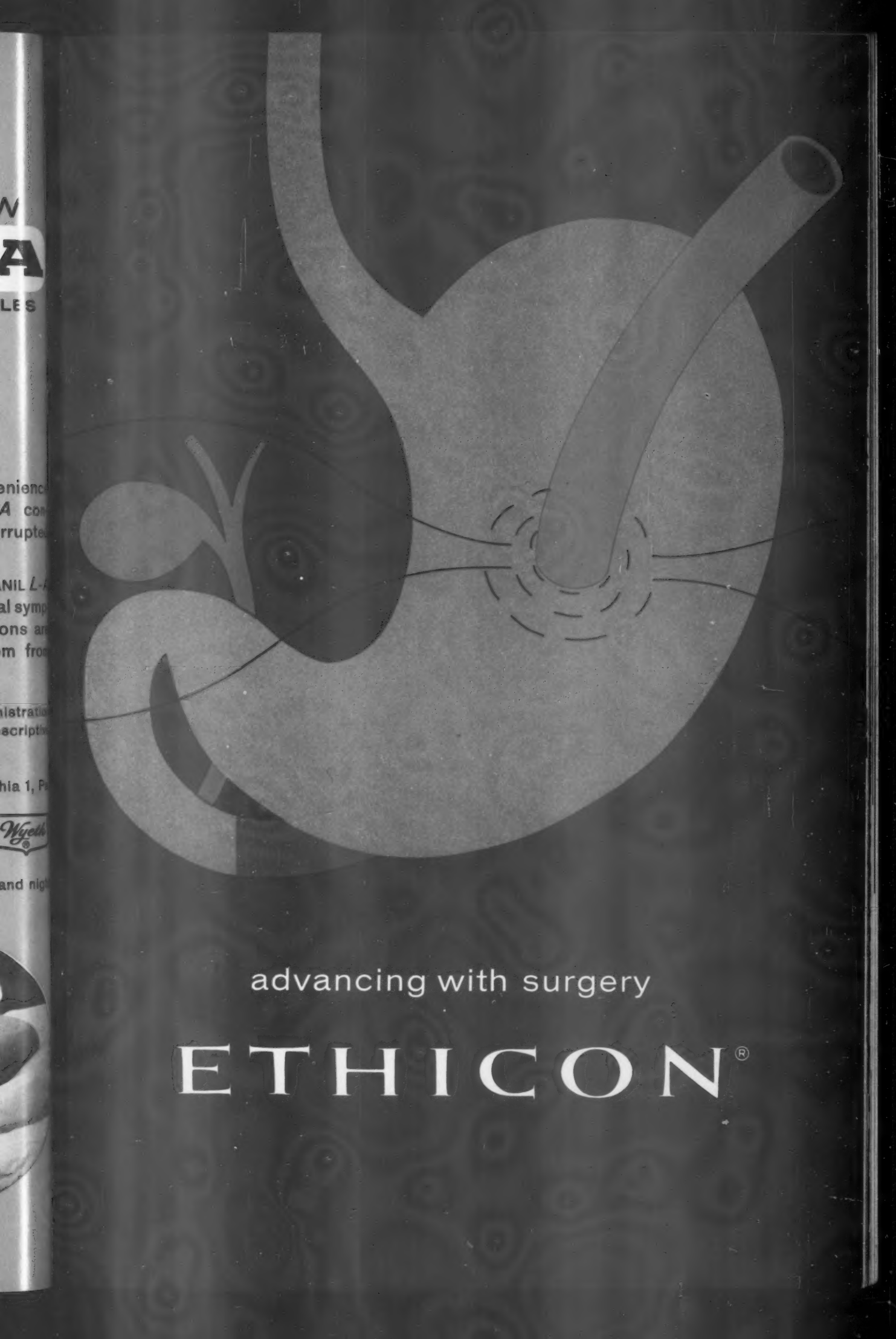
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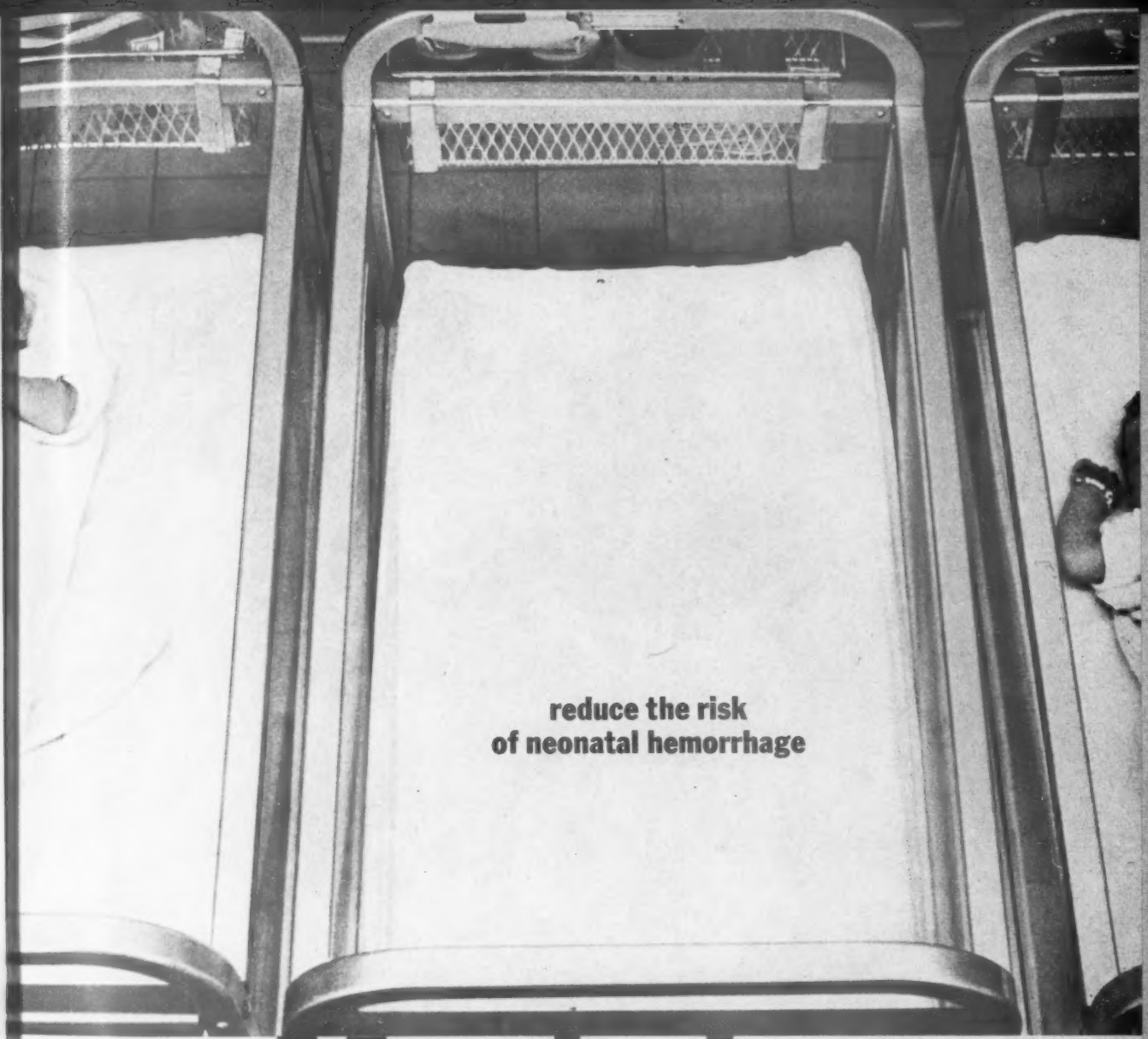
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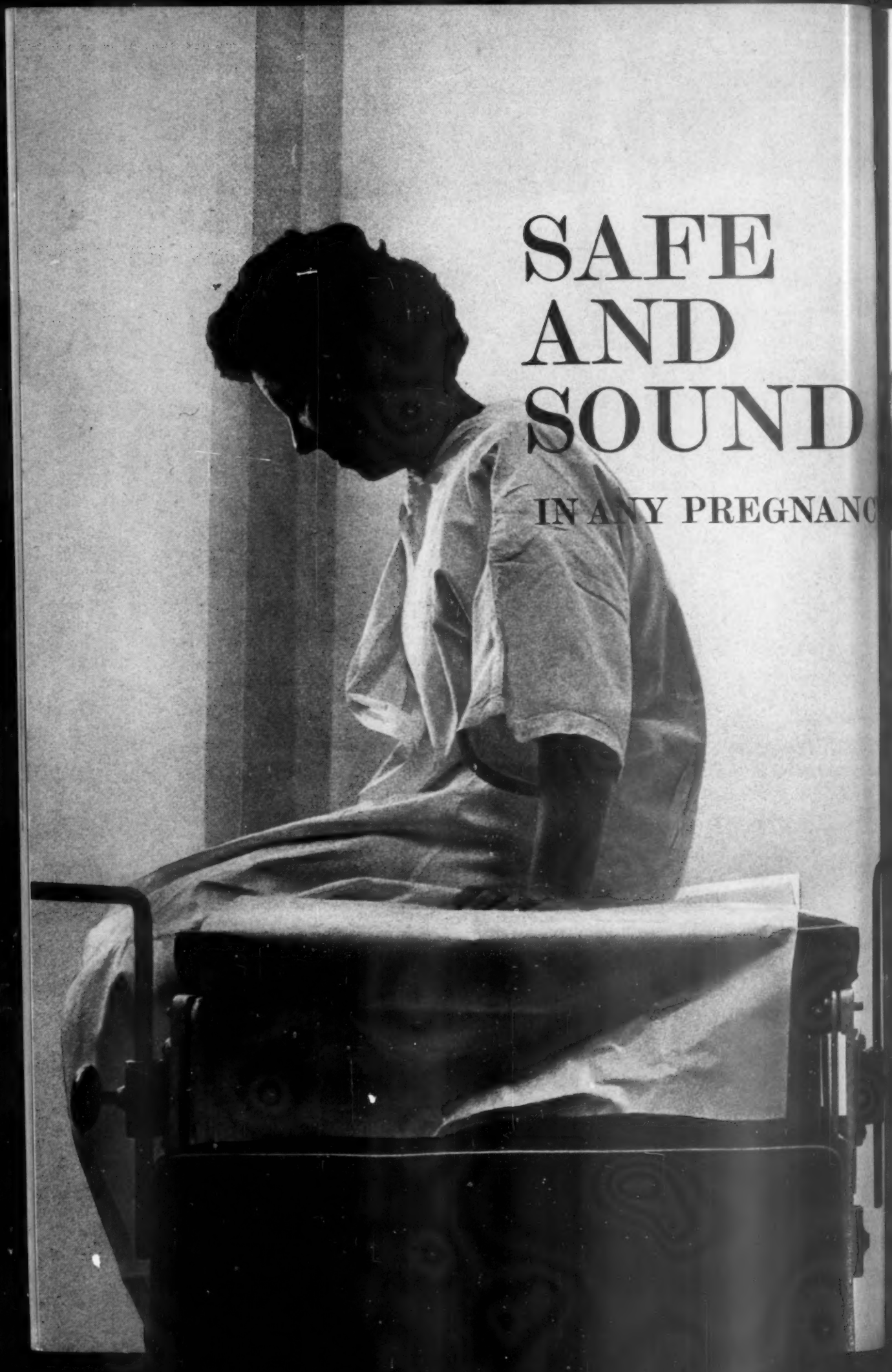
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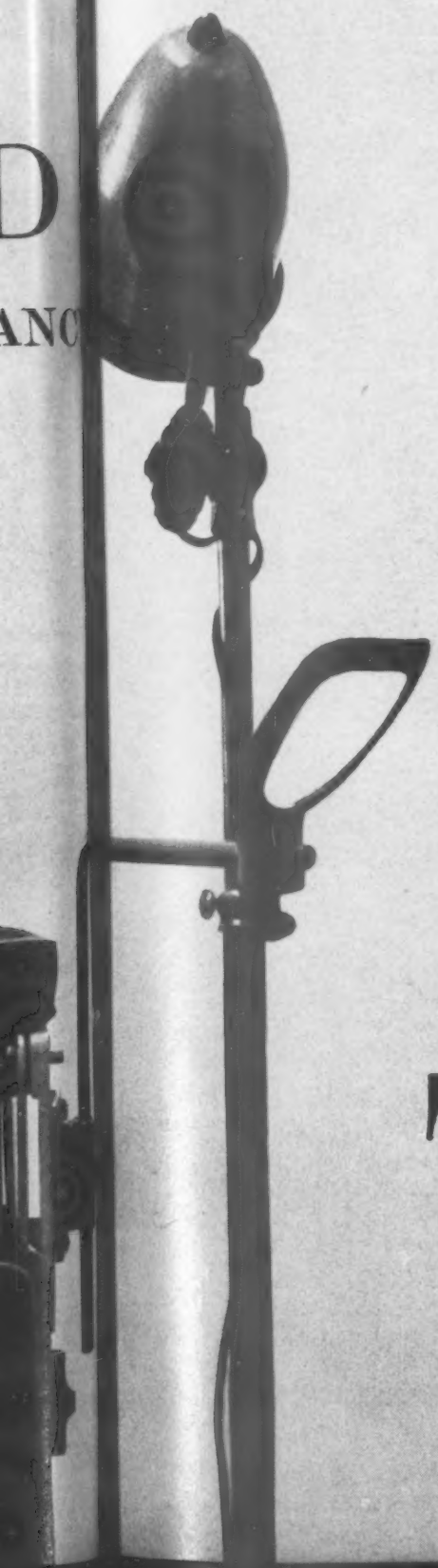
*Council on Drugs: New and Nonofficial Drugs, Philadelphia, J. B. Lippincott Co., 1959, p. 661.

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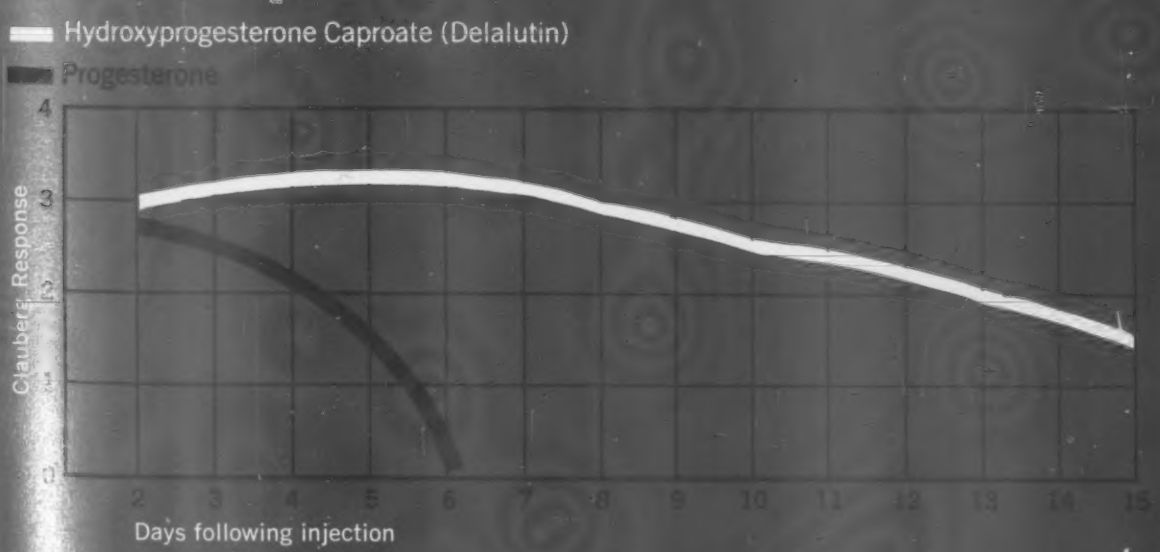
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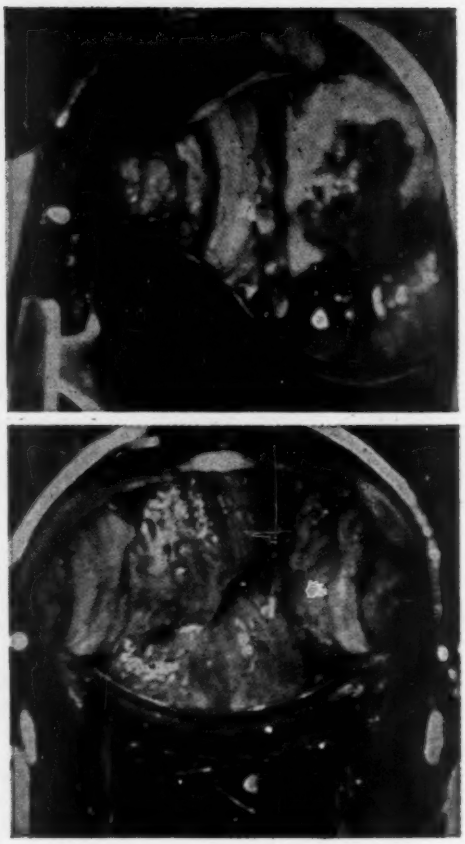
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References: 1. Lee, A. F., and Keifer, W. S.: Northwest Med. *53*:1227 (Dec.) 1954. • 2. Caruso, L. J.: New York J. Med. *58*:1688 (May 15) 1958. • 3. Pace, H. R., and Schantz, S. I.: J.A.M.A. *162*:268 (Sept. 22) 1956.

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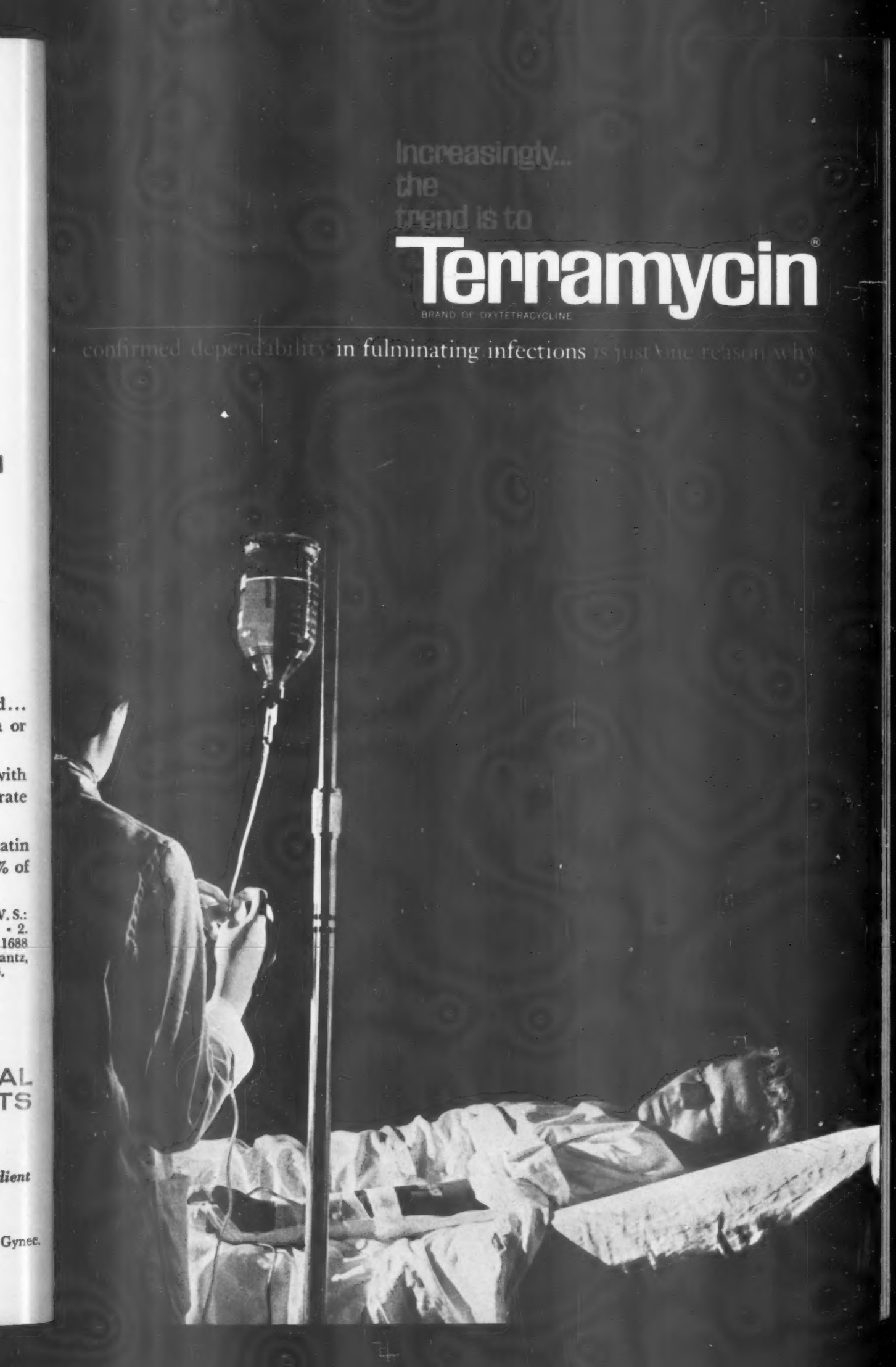
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References: 1. David, N. A.; Porter, G. A.; and Gray, R. H.: Monographs on Therapy 5:60 (Feb.) 1960. 2. Fuchs, M.; Moyer, J. H.; and Newman, B. E.: Op. cit. 5:55 (Feb.) 1960. 3. Ford, R. V.: Current Therap. Res. 2:92 (Mar.) 1960.

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Naturetin Squibb Bendroflumethiazide

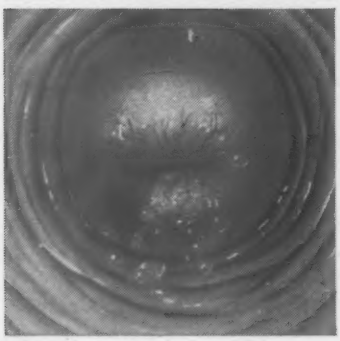
Naturetin c K Squibb Bendroflumethiazide with Potassium Chloride

SQUIBB *Squibb Quality—the Priceless Ingredient*

"NATURETIN" ® IS A SQUIBB TRADEMARK.

SQUIBB DIVISION Olin





in cervicitis and vaginitis

AVC

Cream & Suppositories

stops the torment destroys the cause

Action and Uses: Specific against trichomonads and highly effective in moniliasis, and nonspecific infections. Also for cervicitis and post-cauterization wounds of the cervix. **Cream:** tubes of 4 oz. with or without applicator. Each tube contains: 9-aminoacridine hydrochloride 0.2%, sulfanilamide 15.0%, allantoin 2.0%, with lactose in a water-miscible base buffered with lactic acid to pH 4.5. **Suppositories:** box of 12 with applicator. Each AVC Suppository is equivalent to one applicatorful of AVC Improved Cream. **Dosage:** one applicatorful of AVC Improved Cream or one AVC Suppository intravaginally twice daily.

DIVISION OF RICHARDSON-MERRELL INC.

AVC-745/61 9/61 THE NATIONAL DRUG CO., PHILADELPHIA 44, PA. TRADEMARK: AVC



no longer
detoured
by
diarrhea

DONNAGEL®

Donnatal® with Kaolin and Pectin compound

Robins

DONNAGEL's comprehensive antidiarrheal formulation gives the green light to normal activity, through its fast and dependable control of intestinal hypermotility.

Each 30 cc. (1 fl. oz.) of DONNAGEL contains:

Kaolin	6.0 Gm.	Natural belladonna alkaloids:	
Pectin	142.8 mg.	hyoscyamine sulfate	0.1037 mg.
Phenobarbital (¼ gr.)	16.2 mg.	atropine sulfate	0.0194 mg.
		hyoscine hydrobromide	0.0065 mg.

also available

DONNAGEL WITH NEOMYCIN

DONNAGEL plus neomycin sulfate 300 mg. (as neomycin base 210 mg.) per 30 cc.

DONNAGEL-PG

DONNAGEL plus powdered opium U.S.P. 24.0 mg. per fl. oz. (equivalent to paregoric 6 ml.). This is the usual adult dose.

All three forms available in bottles of 6 fl. oz.

Menopausal distress: a syndrome involving all three levels of the autonomic nervous system

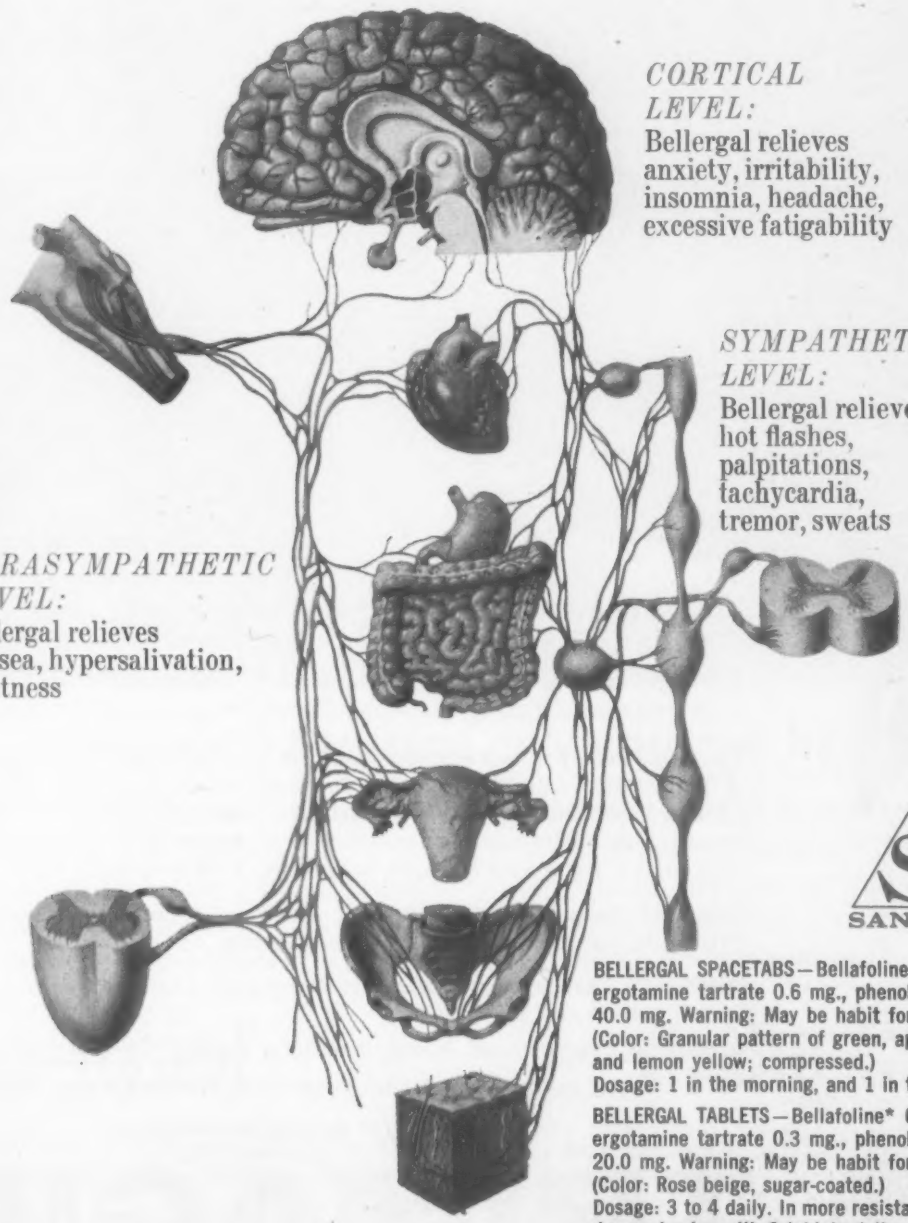
for functional disorders of the menopause

Bellergal®

SPACETABS®

stabilizes the entire autonomic nervous system

(*without disturbing endocrine balance*)



CORTICAL LEVEL:
Bellergal relieves anxiety, irritability, insomnia, headache, excessive fatigability

SYMPATHETIC LEVEL:
Bellergal relieves hot flashes, palpitations, tachycardia, tremor, sweats

PARASYMPATHETIC LEVEL:
Bellergal relieves nausea, hypersalivation, faintness

SANDOZ

BELLERGAL SPACETABS—Bellafoline* 0.2 mg., ergotamine tartrate 0.6 mg., phenobarbital 40.0 mg. Warning: May be habit forming. (Color: Granular pattern of green, apricot and lemon yellow; compressed.)
Dosage: 1 in the morning, and 1 in the evening.

BELLERGAL TABLETS—Bellafoline* 0.1 mg., ergotamine tartrate 0.3 mg., phenobarbital 20.0 mg. Warning: May be habit forming. (Color: Rose beige, sugar-coated.)
Dosage: 3 to 4 daily. In more resistant cases, dosage begins with 6 tablets daily and is slowly reduced.

*LEVOROTATORY ALKALOIDS OF BELLADONNA, AS MALATES.

Hostile Environment...



The fungus, protozoa and bacteria that commonly cause mild and severe leukorrhea require a vaginal pH of 5 to 12 for proliferation.

Trimagill creates a hostile environment! It produces a pH of 2.0 to 2.5—*the three principal infecting organisms cannot live in this acid range.*

Trimagill is well tolerated and has been proved effective in thousands of cases of leukorrhea, vaginitis, cervicitis, moniliasis and mixed infections. No untoward reactions that would require discontinuation of treatment were reported. At times denuded mucous membranes are so irritated that Trimagill may give a *temporary* burning sensation. This is usually short lived.

Trimagill does not foster resistant mutants or result in monilia overgrowth. Trimagill may be used during menstruation.

CONTENTS: Tartaric Acid, Citric Acid, Boric Acid, Dextrose, Potassium Alum, Potassium Bitartrate and Adhesives.

SUPPLIED: Powder: 5-oz. Plastic Insufflator Bottles; Vaginal Inserts: Boxes of 24

NOTE: Consult package circular for information on dosage and instructions for use.

Write for descriptive literature.

TRIMAGILL®

POWDER • VAGINAL INSERTS

THE S. E. MASSENGILL COMPANY

Bristol, Tennessee • New York • Kansas City • San Francisco

*Patent applied for.



...does she know that only **you** can help?

Many patients are unaware that their physician is the best source of contraceptive advice. Your prescription for Ortho-Gynol or Ortho-Creme with a diaphragm assures her the best available contraceptive protection. Accurate tests* for spermicidal potency, as well as years of clinical use, demonstrate that ORTHO contraceptive products are instantaneously spermicidal. The choice between Ortho-Gynol and Ortho-Creme is one of individual esthetic preference.

Ortho-Gynol® vaginal jelly

Ortho®-Creme vaginal cream

*The spermicidal potency of all ORTHO products is controlled by the **Titration Test** and the **Sander-Cramer Test,** which more closely duplicate vaginal conditions during coitus than other tests.

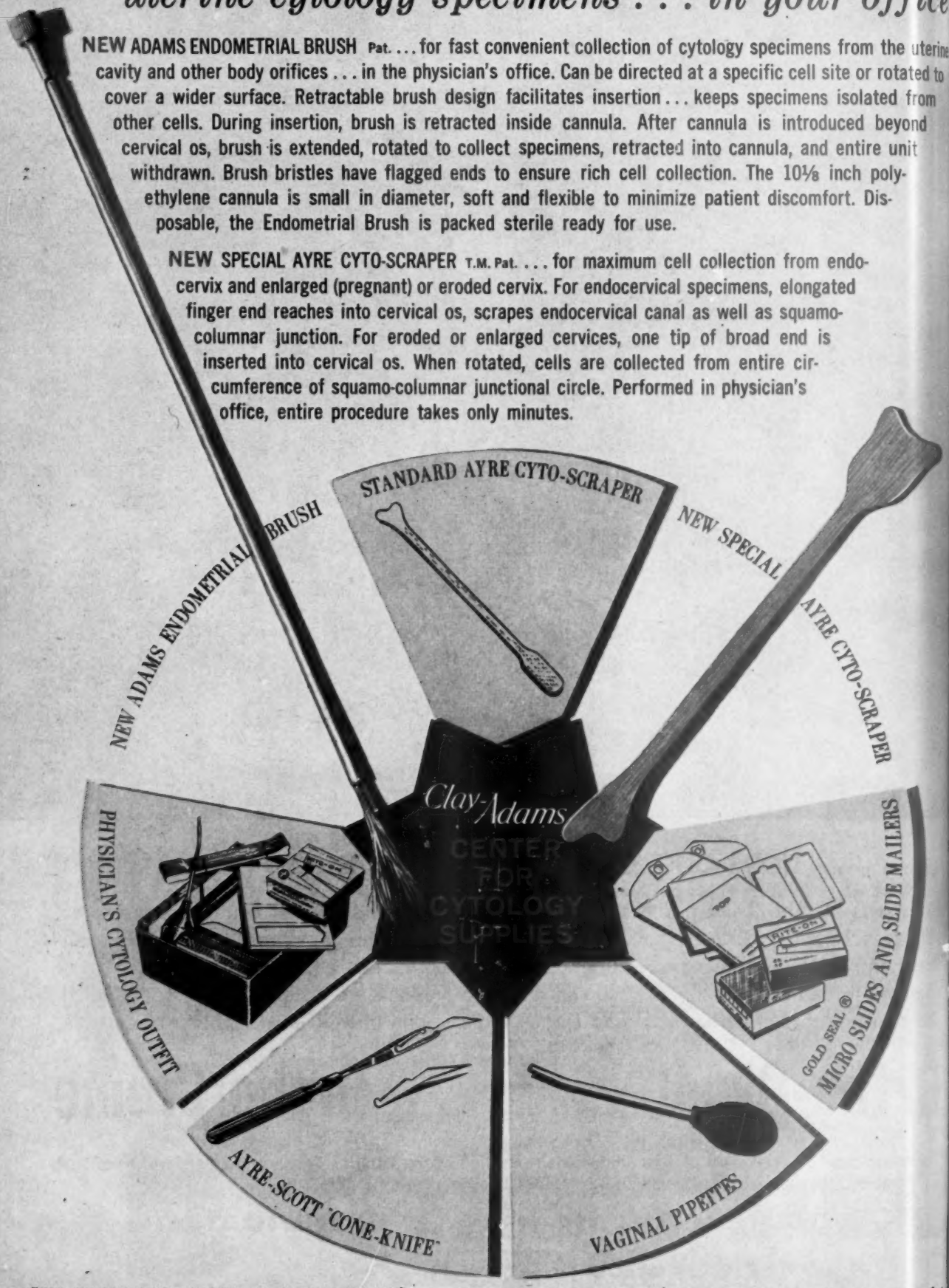
WHENEVER A DIAPHRAGM IS INDICATED

Ortho

two new important instruments for collecting uterine cytology specimens . . . in your office

NEW ADAMS ENDOMETRIAL BRUSH Pat. . . . for fast convenient collection of cytology specimens from the uterine cavity and other body orifices . . . in the physician's office. Can be directed at a specific cell site or rotated to cover a wider surface. Retractable brush design facilitates insertion . . . keeps specimens isolated from other cells. During insertion, brush is retracted inside cannula. After cannula is introduced beyond cervical os, brush is extended, rotated to collect specimens, retracted into cannula, and entire unit withdrawn. Brush bristles have flagged ends to ensure rich cell collection. The 10⅛ inch polyethylene cannula is small in diameter, soft and flexible to minimize patient discomfort. Disposable, the Endometrial Brush is packed sterile ready for use.

NEW SPECIAL AYRE CYTO-SCRAPER T.M. Pat. . . . for maximum cell collection from endocervix and enlarged (pregnant) or eroded cervix. For endocervical specimens, elongated finger end reaches into cervical os, scrapes endocervical canal as well as squamo-columnar junction. For eroded or enlarged cervices, one tip of broad end is inserted into cervical os. When rotated, cells are collected from entire circumference of squamo-columnar junctional circle. Performed in physician's office, entire procedure takes only minutes.



OTHER IMPORTANT CLAY-ADAMS CYTOLOGY SUPPLIES / *Cary Metal Uterine Cannula* / *Mass Screening Kits (packaged to specifications)* / *Papanicolaou Stains* / *Nolan-Budd Cervical Biopsy Curet* / *Medichromes®—full color 2"X2" (35mm Kodachromes on Uterine Cytology — further information write Clay-Adams*

Available from your dealer Clay-Adams *New York 10, N. Y.*

General Use:



The general practitioner, the internist, and the surgeon alike are frequently called on to relieve pain or perform minor surgical procedures that may be successfully managed with the aid of this versatile anesthetic. Consistently effective anesthesia may be expected from Xylocaine because of its fast and profound action and its spreading ability. It is virtually nonirritating to tissues and is relatively nonsensitizing, and possesses a wide margin of safety. For topical anesthesia Xylocaine may be applied as a spray, with cotton swabs, or by packs, as well as by instillation into a cavity and by application onto a surface. Local anesthesia of nerves, plexuses or terminal nerve endings requires individualized volumes and concentrations of Xylocaine, with or without epinephrine. For general use Xylocaine is recommended in concentrations of 0.5%, 1% and 2%, with the 2% solution generally used for nerve block. Minimal volumes of 4% Xylocaine may be used topically in those cases where lower concentrations are ineffective or inadequate. The 4% solution may also be used transtracheally, for retrobulbar injection, and for otological surgery, where small volumes are indicated.

Indications for topical application: Lacerations, abrasions, burns, corneal analgesia, indirect laryngoscopy, pruritus. Indications for injectable anesthesia: suturing, wound closure, causalgia, minor surgery, removal of moles, warts, and cysts, fracture reduction, bursitis, post-traumatic syndrome, herpes zoster.

Xylocaine

INJECTABLE AND TOPICAL ANESTHETIC

Surgery:



Xylocaine is well suited for infiltration and nerve block techniques for a large number of major and minor operative procedures. Xylocaine gives anesthesia of adequate duration, is fast acting with high diffusibility, and its action is predictable. Minimal dosage consistently produces profound anesthesia. The margin of clinical safety is wide, and side effects, considering the extensive use of Xylocaine, are rare. For infiltration, 0.25% and 0.5% solutions are used in volumes of 30 cc. to 100 cc. The 1% solution may be used when smaller volumes of 10 cc. to 30 cc. are to be administered. When a single injection of Xylocaine is used for peridural, spinal and other major nerve blocks, the concentration and volume varies with the type of block and the individual requirements. The total dosage of Xylocaine should *not* exceed 500 mg. when administered with epinephrine, or 300 mg. without epinephrine. Xylocaine is one of the very few anesthetic agents which are effective topically as well as by injection. This is an important advantage in many surgical procedures where mucous membranes of the respiratory, upper gastrointestinal and lower genitourinary tracts, the eye and ear, and the anorectal area are involved. The 2% and 4% concentrations of Xylocaine solutions are used for topical anesthesia. Volumes are adjusted according to the requirements of the surgical procedures being undertaken.

Xylocaine

INFILTRATION, NERVE BLOCK, AND TOPICAL

Obstetrics, Gynecology, Urology:

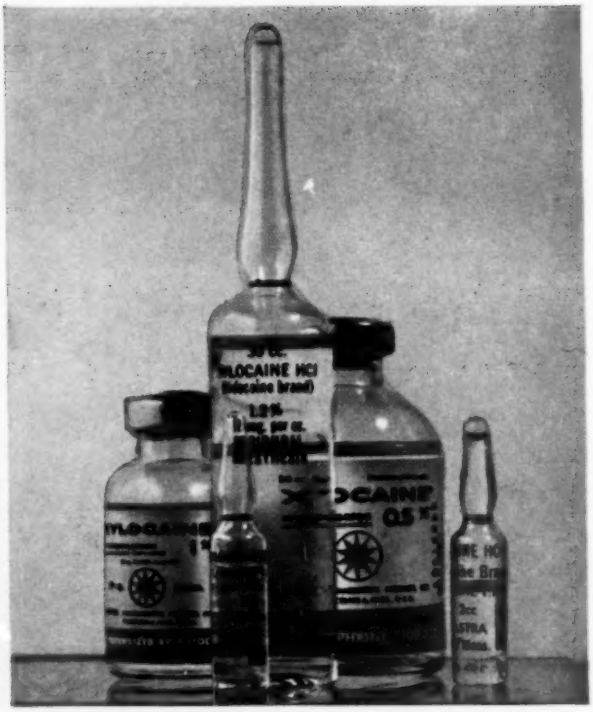


Xylocaine

PERIDURAL, CAUDAL, & SPINAL "SADDLE BLOCK"

Spotty anesthesia and slow onset, once major drawbacks of peridural and caudal techniques, occur only rarely with Xylocaine because of its high esthetic index, wide diffusibility, short latency period, and adequate duration of nerve block. Its relative safety and reliability of performance have caused Xylocaine to be called a "...drug of choice for extradural analgesia."† Because of the wide variation in dosage requirements in extradural anesthesia, there are three concentrations of Xylocaine HCl available for this technique; 1%, 1.5% and 2%. All three concentrations are supplied without epinephrine or with epinephrine 1:200,000, and are dispensed in single dose containers. Operative analgesia is obtained with volumes of 25 cc to 30 cc. of 1% Xylocaine HCl. Concentrations of up to 2% are used for peridural anesthesia where complete muscular relaxation is required; this condition, however, may, in many instances, be achieved with Xylocaine HCl 1.5%. "Xylocaine spinal" may be used with predictable results for obstetrical, gynecological and urological procedures, and for surgery of the lower abdomen and the lower extremities. "Xylocaine spinal" has a low binding affinity that minimizes potential nerve injury. Its anesthetic effect is routinely rapid, profound, well tolerated and free from "spottiness." It is completely stable in the presence of spinal fluid. The anesthetic action of "Xylocaine spinal" is of moderate duration, and ranges from 100 to 140 minutes.

Xylocaine®
(brand of lidocaine*)
local anesthetic



For Infiltration and Nerve Block • Xylocaine HCl 0.5% and 1% without and with epinephrine 1:100,000 in 20 cc. and 50 cc. multiple dose vials. Xylocaine HCl 2% without and with epinephrine 1:100,000 in 20 cc. and 50 cc. multiple dose vials; also 2 cc. ampules (10's and 30's).

For Spinal Anesthesia • Xylocaine HCl 5% with glucose 7.5% (specific gravity 1.030-1.035) in 2 cc. ampules (10's and 100's).

For Peridural Anesthesia • Xylocaine HCl 1%, without epinephrine and with epinephrine 1:200,000, 30 cc.; Xylocaine HCl 1.5% without epinephrine, 20 cc.; Xylocaine HCl 1.5% with epinephrine 1:200,000, 30 cc.; Xylocaine HCl 2% without epinephrine, 10 cc.; and Xylocaine HCl 2% with epinephrine 1:200,000, 20 cc. For Continuous Peridural Anesthesia • Xylocaine HCl 1% without epinephrine, 100 cc. All Xylocaine peridural solutions are dispensed in single dose containers.

For Transtracheal Use, for Retrobulbar Injection and for Otological Surgery • Xylocaine HCl 4% without epinephrine in 5 cc. ampules (10's).

For Topical Application • Xylocaine HCl 0.5% and 1% without and with epinephrine 1:100,000 in 20 cc. and 50 cc. multiple dose vials. Xylocaine HCl 2% without and with epinephrine 1:100,000 in 20 cc. and 50 c multiple dose vials; also 2 cc. ampules (10's and 30's Xylocaine HCl 4% without epinephrine in 50 c screw-cap bottles. (NOTE: This dispensing form never to be used for injection.) Also available f topical use, Xylocaine Ointment 2.5% and 5 Xylocaine Jelly 2%, and Xylocaine Viscous 2%.

Write for additional complete information concerni specific Xylocaine usage.

†*Bryce-Smith, R.: Local analgesic drugs, Brit. M.J.* 1:*1039 (Ap 2) 1960.*

Contraindications: Injection: Sepsis in region of pr posed injection, severe shock and heart block. Topical Traumatized mucosa and sepsis in the region of th proposed application.

Precautions: In general, reactions and complicatio are best averted by using the lowest concentration a volume of the anesthetic agent that will produce th degree of blockade desired. Injections should alwa be made slowly and with frequent aspiration. Inst lations should always be made slowly and with cautio Except in those cases where vasopressor drugs a contraindicated, epinephrine should be used, in c centrations not to exceed 1:100,000, to prolong an thesia and to reduce systemic absorption. Wh Xylocaine is used with epinephrine, the caution r quired by any vasopressor drug is in order, especia in cases of patients with hypertension, diabetes a thyrotoxicosis.

Reactions and their management: Untoward effe may occur due to unusual sensitivity, faulty te nique, overdosage, and inadvertent intravascular subarachnoid injection. The type of toxic reaction unpredictable and depends on dosage, rate of abso tion and status of the patient. Reactions due systemic absorption are primarily of two types a referable to stimulation and/or depression of th cerebral cortex and medulla.

A. Slow onset—stimulation leading to: nervousnes dizziness, blurred vision, nausea, tremors, convu sions, hypotension, cardiovascular depression a respiratory arrest.

B. Rapid onset—depression leading primarily t respiratory arrest, cardiovascular collapse and ca diac arrest. This type of reaction calls for extrem preparedness—symptoms occur rapidly and with li tle warning. With prompt recognition and treatmen symptoms usually are readily controlled. Maintain a patent airway and administering oxygen assure adequate ventilation; administration of a sma amount of a short-acting barbiturate or a musc relaxant controls convulsions; vasopressors, used a indicated, support circulation.

Astra Pharmaceutical Products, Inc.
Worcester 6, Massachusetts

Printed in U.S.A. Copyright 1961 *U.S. Pat. No. 2,441,498 Made in U.S.



Natalins® tablets

Comprehensive vitamin-mineral support, pre- and post-natal

Only one Natalins tablet per day provides generous amounts of iron, calcium, and vitamin C, plus 8 other important vitamins. This special formula helps assure, in multiparas, the extra nutritional protection they—particularly*—need. It naturally follows that this formulation will be adequate for the primigravida.

*Taylor, J. B., and Torpin, R.: Am. J. Obst. & Gynec. 61:71-74 (Jan.) 1951.

With their new smooth coating, Natalins tablets are easier to swallow—and they disintegrate rapidly and fully for maximum utilization.

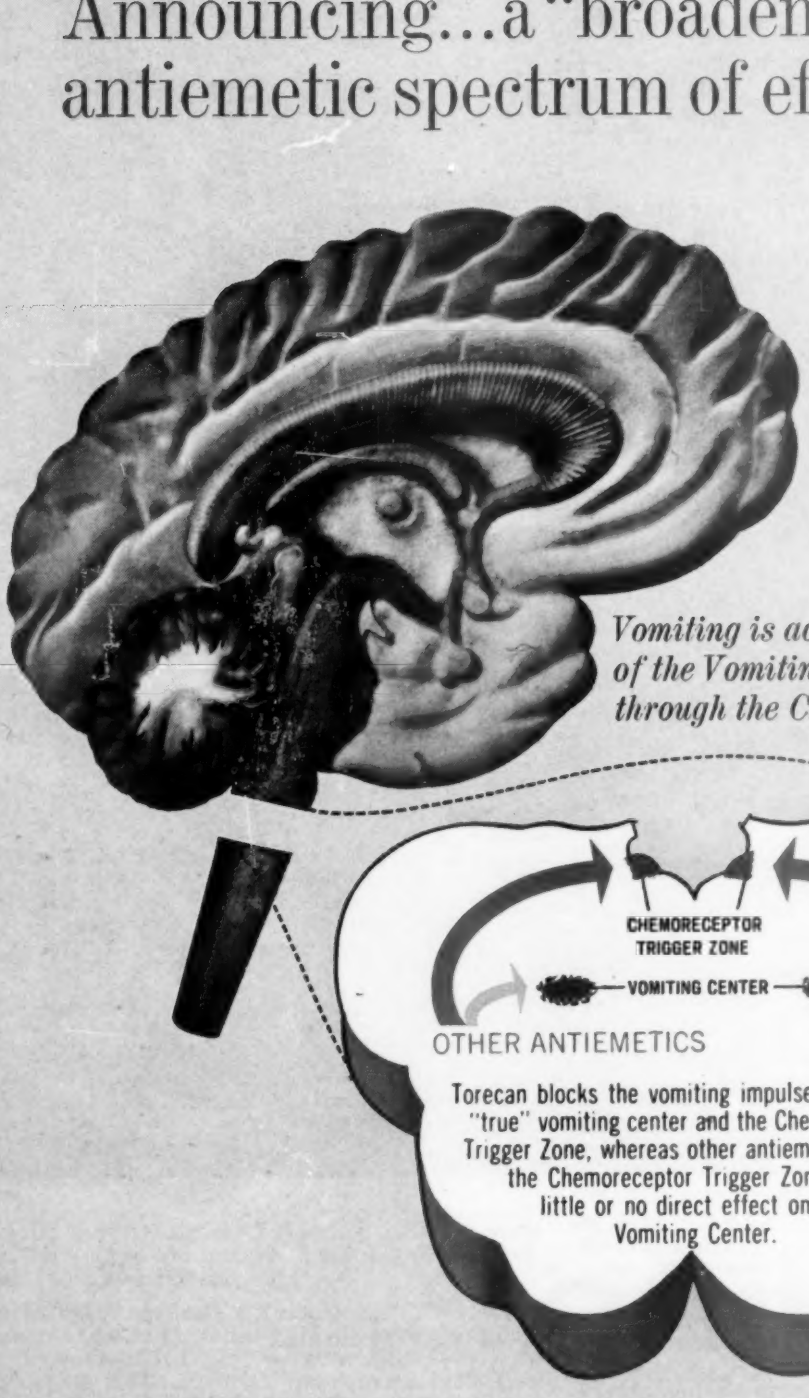
For your convenience in specification, Natalins tablets and Natalins Basic tablets have replaced all other Natalins formulations.

52461

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Symbol of service in medicine

Announcing...a "broadening of the antiemetic spectrum of effectiveness"



Vomiting is activated by stimulation of the Vomiting Center, either directly through the Chemoreceptor Trigger Zo

"Thiethylperazine dimaleate [TORECAN] inhibits apomorphine vomiting [apomorphine elicits vomiting solely through the Chemoreceptor Trigger Zone[2,3,4]] in an even more pronounced manner than the well-known strong antiemetic, prochlorperazine. Thiethylperazine dimaleate also antagonizes oral copper sulfate [copper sulfate may activate the Vomiting Center directly or may act via the Chemoreceptor Trigger Zone]. Interestingly, only slightly higher dosages are needed for this than for the inhibition of apomorphine vomiting, whereas far higher dosages are required of other phenothiazines. This peculiarity of thiethylperazine of influencing not only the trigger zone, but also the vomiting center is of much therapeutic interest because of the broadening of the antiemetic spectrum of effectiveness."[1]

"When evaluating new antiemetic agents, it is necessary to pay close attention to the associated effects on the central and autonomic nervous systems. The aim is to find agents which will specifically depress the emetic mechanism with minimal effects elsewhere."[8]

TORECAN

provides specific antiemetic action with minimal "spillover" effects:

Tranquilizing or sedative action	Insignificant
Potentiation of sedative and anesthetic drugs	Only slight potentiation; less than with other phenothiazine antiemetics
Extrapyramidal symptoms, such as motor restlessness, muscular rigidity, parkinsonism, etc.	Rarely at dosage levels of 30-50 mg. per day
Cardiovascular effects (hypotension, cardiac acceleration)	Rare; less than with other phenothiazine antiemetics
Liver, blood, or renal toxicity	None reported
Other side effects: dizziness, dry mouth, weakness, fatigue, blurring of vision, headache, insomnia, constipation or diarrhea	Rare

"an extremely effective antiemetic in a large number of clinical conditions"[5]

Nausea and Vomiting of Pregnancy[6]

Nausea and Vomiting Associated with Gastroenteritis and Colitis[5,6,7]

Nausea and Vomiting due to Radiation and Nitrogen Mustard Therapy[1]

Postoperative Nausea and Vomiting[5]

Nausea and Vomiting Associated with Miscellaneous Non-inflammatory Conditions[5,6,7]

Nausea and Vomiting Associated with Labyrinthine Disturbances

Adult Dosage: Oral: 1 tablet 3 times daily
Intramuscular: 10 — 20 mg. daily

Supply: Tablets, 10 mg.; Ampuls, 2 cc. (10 mg.), each cc. contains 5 mg.

Precautions: It is obvious that, before using an antiemetic, clinical judgment must be exercised in determining whether vomiting represents a warning of organic abnormality and that this must first be recognized before employing a potent antiemetic such as TORECAN. Drowsiness and/or dryness of the mouth may occur with doses above 30 mg. daily. While no hepatic, hematopoietic or renal toxicity have been reported at recommended dosage levels, it should be remembered that these reactions may occur with phenothiazines. Orthostatic hypotension may be manifested at higher dose levels. TORECAN is contraindicated in severely depressed or comatose states. In excessive doses, TORECAN may produce extrapyramidal stimulation with the varied symptom complex characteristic of this complication. Ampuls are recommended for **intramuscular injection only.**

References: 1. Codiga, V. A.: A new antiemetic for the treatment of nausea and vomiting associated with roentgen therapy, Int. Rec. Med., 174:375 (June) 1961. 2. Wang, S. C. and Borison, H. L.: The vomiting center: its destruction by radon implantation in dog medulla oblongata, Am. J. Physiol. 166:712 (1951). 3. Wang, S. C. and Borison, H. L.: A new concept of organization of the central emetic mechanism: recent studies on the sites of action of apomorphine, copper sulfate and cardiac glycosides, Gastroenterol. 22:1 (1952). 4. Wang, S. C. and Glaviano, V. V.: Locus of emetic action of morphine and hydergine in dogs, J. Pharmacol. & Exper. Therap. 111:329 (1954). 5. Browne, D. C. and Sparks, R.: Vomiting mechanisms: a clinical study of thiethylperazine, South. M.J., 54:(Sept.) 1961. 6. Browne, D. C. and Sparks, R. D.: Nausea and vomiting, study of thiethylperazine, Scientific Exhibit, American Medical Association Clinical Meeting, Washington, D.C., Nov. 28 (1960). 7. Maritano, M., Guerrieri, S., Menesini, R.: Prophylaxis and therapy of vomiting, Minerva anest. 26:343 (1960). 8. Modell, W.: Drugs of choice 1960-1961. C. V. Mosby Co., St. Louis, 1960, p. 339.

SANDOZ — ORIGINAL RESEARCH SERVING THE PHYSICIAN

cts on the True Vomiting Center

TORECAN®

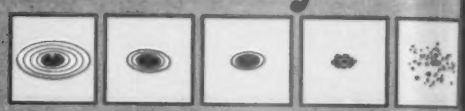
Thiethylperazine Maleate

2-ethyl-mercapto-10-[3'-(1"-methyl-piperazinyl-4")-propyl-1'] phenothiazine dimaleate

Bendectin at bedtime prevents morning sickne



here's why:



BEDTIME EARLY MOR

BENDECTIN release assures peak action when sh needs it most... *first thing in the morning!*

"...I have gained the best results wit [BENDECTIN]...Because these tablets ha a protective coating...the dose taken night becomes effective in the morning."

BENDECTIN

Double-blind study shows BENDECTIN effecti in 94% of patients.[2] In compiled repor s, effe tive in 1220 of 1267 patients.[2-6]

With BENDECTIN, there are no phenothiazin like side effects.

And BENDECTIN costs less per day than a qua of milk.

Dosage: Two tablets at bedtime.

Supply: Bottles of 100 and 500.

Formula: Each special coated tablet contai Bentyl (dicyclomine) hydrochloride, 10 mg Decapryn (doxylamine) succinate, 10 mg Pyridoxine hydrochloride, 10 mg.

References: 1. Middleton, T. F.: Postgrad. Med. 24:6 1958. 2. Geiger, C. J., *et al.*: Obst. & Gynec. 5:668, 19 3. Nulsen, R. O.: Ohio State M. J. 53:665, 1957. 4. Tow J. E.: Internat. Rec. Med. 171:583, 1958. 5. Woodhall, R. Western Med. 1:13,1960. 6. Personal communications: 1956

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Merrell
SINCE 1828

THE WM. S. MERRELL COMPANY
Division of Richardson-Merrell Inc.
Cincinnati, Ohio/Weston, Ontario

TRADEMARKS: BENDECTIN®, BENTYL®, DECAPRYN®

RAMSES® prophylactics—to prevent re-infection in vaginal trichomoniasis.

Confirming the views of many others,[1-3] Romney[4] has recently pointed out that *Trichomonas* may be harbored asymptomatically in the male and transmitted to the female to produce a resistant vaginitis; and that "... therapy which is directed solely towards the female patient is unrealistic and ineffectual." For this reason, the husband's cooperation must be enlisted in order to end this cycle of infection and re-infection.



Husbands appreciate RAMSES, the prophylactic with "built-in" sensitivity.

The exquisite sensibility preserved by this tissue-thin, natural gum-rubber sheath of amazing strength and solid clinical reliability places RAMSES almost out of human awareness. Without imposition or deprivation for the sake of cure, the routine use of RAMSES with "built-in" sensitivity is readily adopted, even by the husband who fears loss of sensation.

1. Karnaky, K. J.: South. M. J. *51*:925 (July) 1958.
2. Giorlando, S. W., and Brandt, M. L.: Am. J. Obst. & Gynec. *76*:666 (Sept.) 1958.
3. Davis, C. H., and Grand, C. G.: Am. J. Obst. & Gynec. *68*:559 (Aug.) 1954.
4. Romney, S. L.: M. Sc. *8*:235 (Aug. 25) 1960.

RAMSES®
PROPHYLACTICS

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only 2 seconds to specify maximum QUALITY

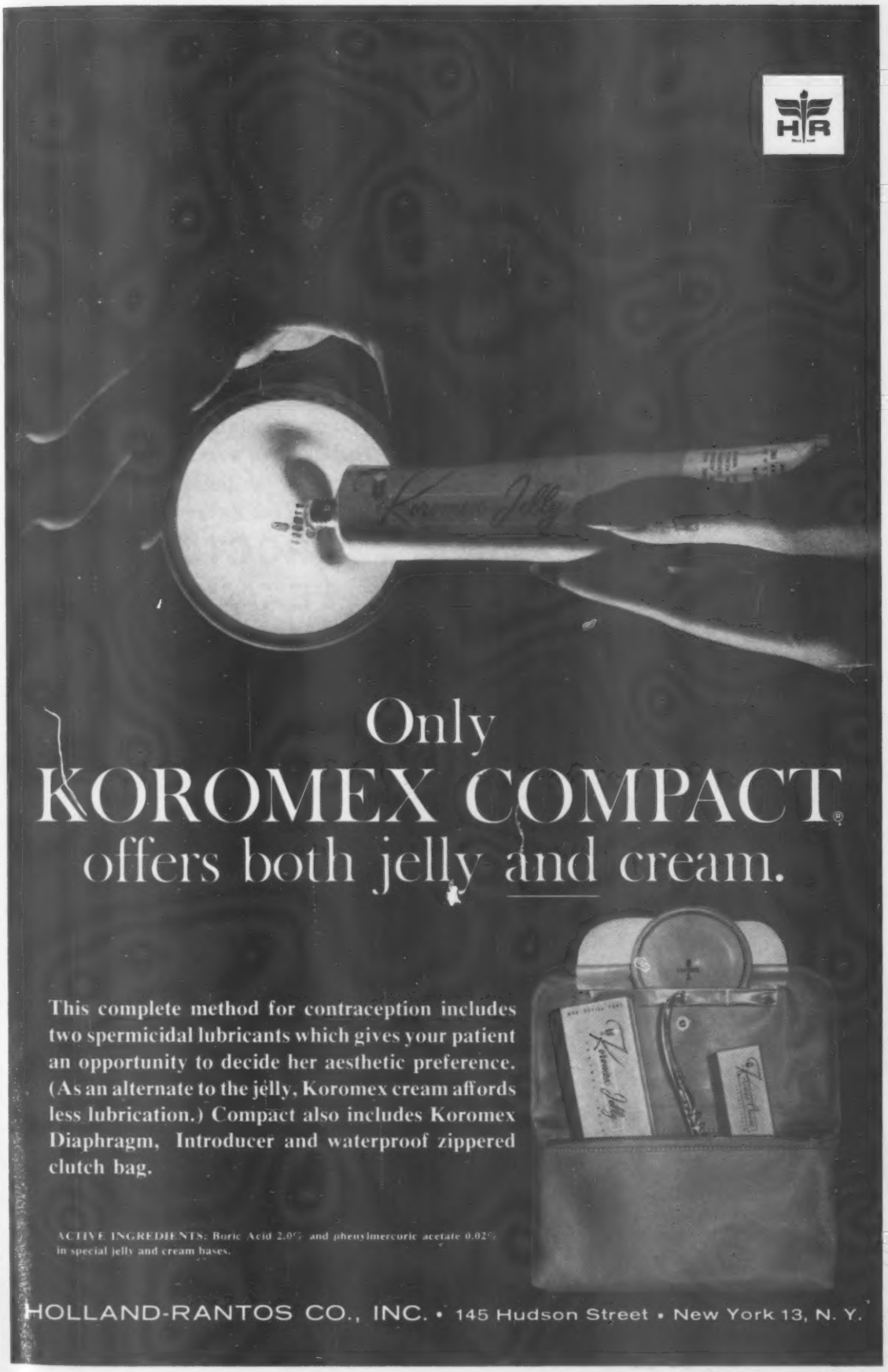


Only 2 seconds are needed to write, "Thyroid *Armour*" on a prescription: a small investment in time, but one that offers big advantages to your patients. In Thyroid *Armour* you get maximum quality insured by consistently high standards of preparation. Over 75 years' experience is behind the Armour brand.

THYROID U. S. P.

Thyroid Tablets (Armour) are prepared from fresh selected glands, desiccated and standardized by official U.S.P. method to contain 0.2 per cent of iodine in thyroid combination. Thyroid Powder U.S.P. (Armour) is standardized and of uniform potency. USES: Thyroid deficiencies, cretinism, myxedema, nodular goiter (nontoxic), non-nodular goiter. A variety of clinical conditions will respond to the use of Thyroid (Armour) when subclinical hypothyroidism is involved. DOSAGE: ¼ to 5 grains daily as required by clinical condition. Therapeutic effect develops slowly and lasts for two months or longer. Thus the daily dose may be given as a single dose (preferably in the morning) rather than several times daily. Patients treated with thyroid should be continuously under the physician's observation. CONTRAINDICATIONS: Heart disease and hypertension, unless the metabolic rate is low. SUPPLIED: Tablets—bottles of 100, 1000 and larger; potencies of ¼, ½, 1, 2 and 5 grains. Powder—1 oz., 4 oz. and 1 lb. bottles.

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Only
KOROMEX COMPACT®
offers both jelly and cream.
This complete method for contraception includes two spermicidal lubricants which gives your patient an opportunity to decide her aesthetic preference. (As an alternate to the jelly, Koromex cream affords less lubrication.) Compact also includes Koromex Diaphragm, Introducer and waterproof zippered clutch bag.
ACTIVE INGREDIENTS: Boric Acid 2.0% and phenylmercuric acetate 0.02% in special jelly and cream bases.
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In 1961, you, the nation's physicians, will diagnose an estimated 70,000 cases of cancer of the colon and rectum. Although potentially this is a highly curable cancer, each year more than two thirds of such patients die of the disease. Thousands are lost needlessly. They could be saved by proper medical treatment of the disease, found by annual examination, in its presymptomatic and most curable stage. The regular health checkup and alertness to first symptoms are great life-savers. To help bring such patients to you *in time,* the American Cancer Society has developed a forceful, comprehensive public education program on cancer of the colon and rectum. The Society's newest film, *Life Story* dramatizes for the public the importance of the inclusion of digital and

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In this, as in the preparation of all of its life-saving educational materials, the Society is aided by the best medical and lay experts available. The physician and the layman in the American Cancer Society are truly partners for life.



AMERICAN CANCER SOCIETY



PROVEN SUPERIOR KNOT STRENGTH IN NEW HIGH TENSILE SURGICAL GUT

CYANAMID | SURGICAL PRODUCTS DIVISION

*REPRESENTS AVERAGE STRENGTH OF PERIODIC SAMPLES OF A YEAR'S SUPPLY.

new processing methods for absolute uniformity: complete production control from raw animal gut to finished strand provides suture strands of uniform diameter, maximum knot strength and predictable performance.

satin matte finish: an exclusive new finishing process eliminates fraying and creates a softer, smoother strand that assures greater knot security. Increased pliability facilitates handling and tying.

controlled absorption: carefully controlled chromic processing maintains in situ gut strength during wound healing. Rigid laboratory digestion tests assure a uniform rate of absorption and compatibility with tissue. Surgical gut sutures are available in plain, mild chromic and medium chromic strands.

...combined with stronger, sharper ATRAUMATIC® Needles—New drilled end design permits uniform tempering of entire needle for greater needle strength. The needle holder may be placed far back on the needle shaft for greater tissue "bite". Inner curvature of needle has center flattened surface all the way back on the needle shaft for sure grip in holder to prevent twisting and turning of needle.

NEW HIGH TENSILE SURGICAL GUT

available in the safer product protector, SURGILOPE SP® Sterile Suture Strip Pack—winner of the 1960 Packaging Institute Award for the most outstanding advance in packaging technology.

CYANAMID | SURGICAL PRODUCTS DIVISION

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Menopausal Patients are Pleased with ESTROSED® Therapy

Estrogenic deficiencies and emotional disturbances are successfully managed with flexible, potent Estrosed



- Vasomotor instabilities respond to ethinyl estradiol, ". . . one of the most potent estrogens known."[1]
- Nervousness and insomnia are quieted with reserpine, ". . . useful chiefly for its psychotherapeutic sedative action in the symptomatic management of patients with anxiety or tension psychoneurosis . . ."[2]

Your results with Estrosed therapy will be gratifying. Estrosed contains 0.01 mg. ethinyl estradiol and 0.1 mg. reserpine.

Low Dosage—Economical Therapy

Suggested dosage: One tablet three times daily until symptoms are controlled. Thereafter reduce to maintenance dosage of one tablet every day or two, as may be required.

1. N.N.R., 1959, 515; 2. Ibid., 376

CHICAGO PHARMACAL CO.

5547 N. Ravenswood Ave., Chicago 40, Illinois

CONTRAINDICATIONS: In patients with history of mental depression, peptic ulcer, or ulcerative colitis, reserpine in maintenance doses greater than 0.25 mg. daily is contraindicated and smaller doses should be used with great caution. Reserpine should be discontinued 2 weeks prior to elective surgery. In case of emergency surgery, a vagal blocking drug should be given to counteract the potentiation of the hypotensive effect of reserpine by certain anesthetic agents.

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Gentlemen: Please forward generous supply of Estrosed ☐
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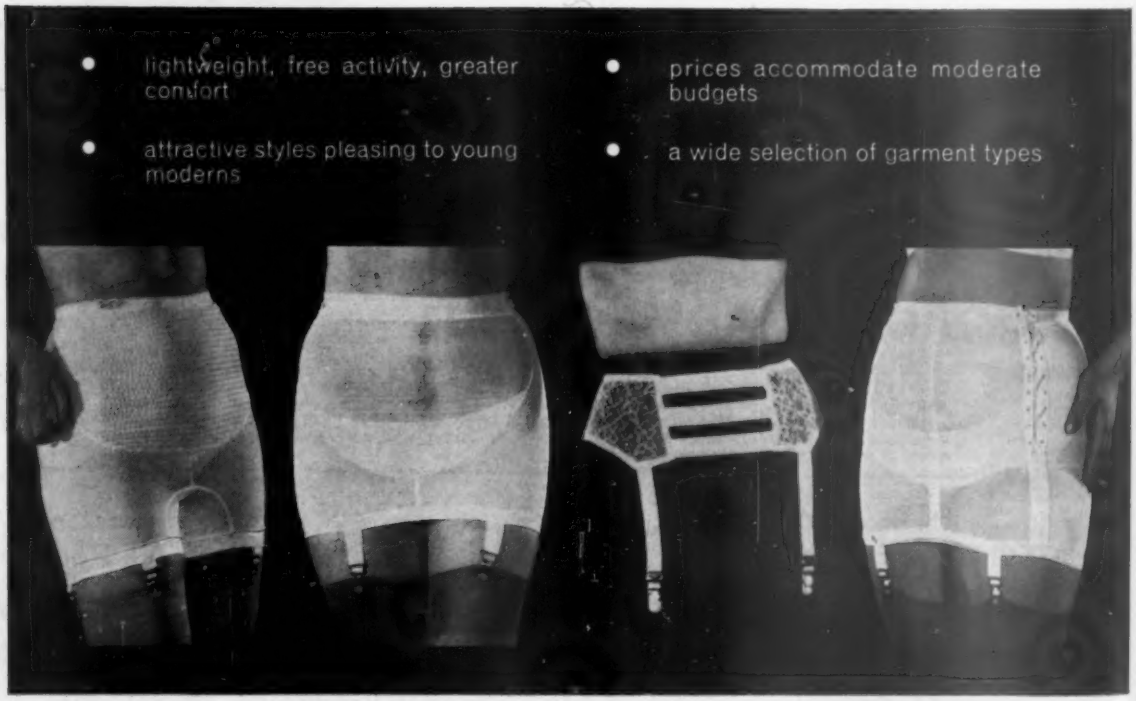
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PRENATAL GARMENTS

lightweight prenatal garments for patients not requiring sturdy support

Prescribe Camp lightweight garments for those patients who may not need the functional, supporting type garment. Camp offers prenatal garments ranging from a garter belt to hold up the patient's hose to fashionable non-supporting girdles and panty girdles priced from a surprisingly low $2.95 at retail. The wide variety of fabrics and types available, the fine quality of the garments, combined with the touch of glamor women desire, creates physical and psychological benefits important to patient satisfaction.

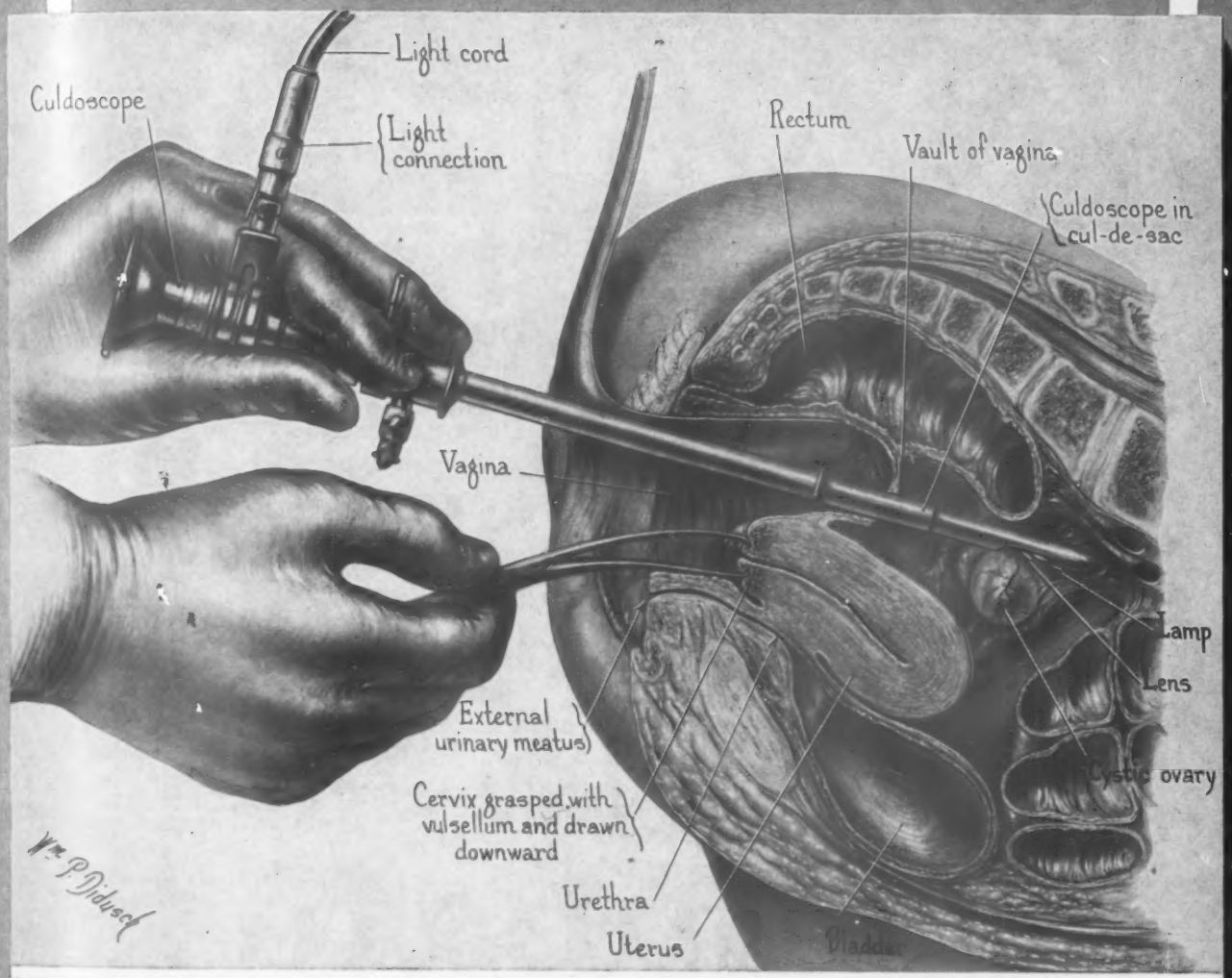
For patients requiring more than just casual support, a series of moderate and sturdy supporting garments are also available. Such supports help prevent undue stretching of the abdominal walls, aid in preventing strain of the sacro-iliac joints and support the back adequately.



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CAMP

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CULDOSCOPE



The illustration above shows the Decker Culdoscope in endoscopic visualization of the female pelvic structures by the vaginal route. It permits direct study of pelvic tumors, ovarian pathologies, ectopic pregnancy, endometriosis, pelvic and intestinal adhesions, etc.

ESTABLISHED IN 1900 — BY REINHOLD WAPPLER

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URETHRAL ANTIBACTERIAL LUBRICANT STERILE

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'Aerosporin'® brand Polymyxin B Sulfate . . . 5,000 Units
Benzalkonium Chloride . . . . . .330 mcg.
Available in 5 Gm. tube with separate sterile urethral applicator tip.



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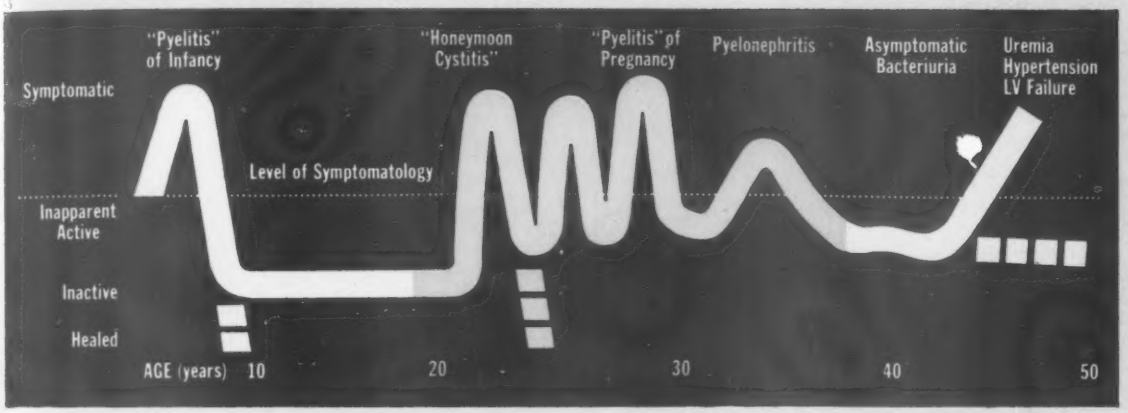
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Sterile ■ Transparent ■ Nonirritating ■ Adheres firmly to instruments ■ Washes off easily ■ No unpleasant odor ■ Suitable viscosity for optimum lubrication

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Natural History of Pyelonephritis



". . . the theme that runs through the carefully taken history of most uremic patients with chronic pyelonephritis—the burning on urination of infancy, the chills and fever in childhood, the 'honeymoon' pyelitis, the recurrent urethritis treated so well and often locally—and yet the termination in uremia."[1]

the child-bearing age—a second major stage for urinary tract infection

"The fact that the many cases of chronic and finally, lethal, upper urinary infections in women begin or recur during gestation is especially challenging."[2] "We now believe that all prepartum women should have one quantitative urine culture as part of their medical management."[3]

Furadantin—when pregnancy initiates (or activates) urinary tract infection

In a study of 104 pregnant women with urinary tract infections: "FURADANTIN was highly effective in the treatment of these infections during all stages . . . and frequently offers the best chance of effecting a clinical cure."[4]

FURADANTIN DOSAGE DURING PREGNANCY AND THE PUERPERIUM: The average dose is one 100 mg. tablet 4 times daily, given with meals and with food or milk on retiring, to prevent nausea. For acute, uncomplicated infections, 50 mg. q.i.d. may be administered. If improvement does not occur in 2 or 3 days, increase dosage to 100 mg. q.i.d.

SUPPLIED: Tablets, 50 mg. and 100 mg. Oral Suspension, 25 mg. per 5 cc. tsp.

REFERENCES: 1. Birchall, R.: Am. Practit. *11*:918, 1960. 2. Benson, R. C., and Mitchell, J. C.: Clin. Obstet. Gynec. *1*:97, 1958. 3. Favour, C. B.: Southern Med. J. *54*:848, 1961. 4. Nesbitt, R. E. L., Jr., and Young, J. E.: Obstet. Gynec. (N. Y.) *10*:89, 1957.

Complete information in package insert or on request to the Medical Director.

EATON LABORATORIES, Division of The Norwich Pharmacal Company, NORWICH, NEW YORK

To cure or control infection throughout the urinary system at every age of life... at every stage of infection

Furadantin®

brand of nitrofurantoin



PHENAPHEN®

- More satisfactory than "the usual analgesic compounds" for relieving pain and anxiety.[1]
- More effective than a standard A.P.C. preparation for relief of moderate to severe pain.[2]

Each PHENAPHEN *capsule contains:*

Acetylsalicylic acid (2½ gr.)	162 mg.
Phenacetin (3 gr.)	194 mg.
Phenobarbital (¼ gr.)	16.2 mg.
Hyoscyamine sulfate	0.031 mg.

Also available:

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¼ GR. (16.2 mg.) Phenaphen No. 2
PHENAPHEN with CODEINE PHOSPHATE
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PHENAPHEN with CODEINE PHOSPHATE
1 GR. (64.8 mg.) Phenaphen No. 4

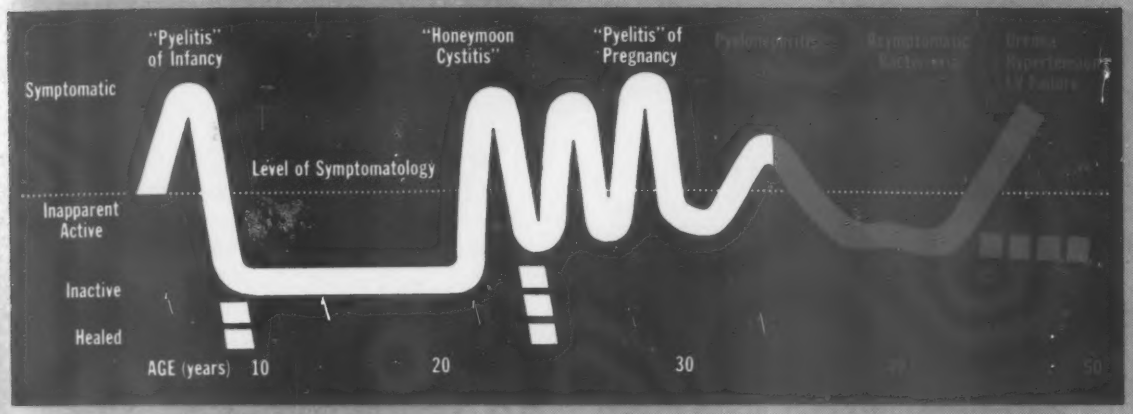
Bottles of 100 and 500 capsules.

1. Meyers, G. B.: Ind. Med. & Surg. 26:3, 1957. 2. Murray, R. J.: N. Y. St. J. Med. 53:1867, 1953.

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Natural History of Pyelonephritis



"... the theme that runs through the carefully taken history of most uremic patients with chronic pyelonephritis—the burning on urination of infancy, the chills and fever in childhood, the 'honeymoon' pyelitis, the recurrent urethritis treated so well and often locally—and yet the termination in uremia."[1]

during the middle and later years—relapse, reinfection, renal failure

"... the physician treating a patient with established chronic urinary tract infection faces a grave problem of management."[2]

Furadantin—to preserve function; to prolong life

"... certain patients with renal insufficiency derived measurable benefit from prolonged nitrofurantoin treatment; as infection was suppressed their renal function improved. This effect was sufficiently pronounced to be considered an important component of the management of uremia accompanying chronic pyelonephritis."[2]

FURADANTIN DOSAGE IN LONG-TERM THERAPY: "With normal renal function, the dosage schedule of 50 mg. four times daily in adults gave urinary nitrofurantoin concentrations that usually exceeded 5 mg. per 100 mg. throughout the day. This level was thought to be sufficient, on the basis of bacterial sensitivity determinations."[3] In refractory cases, 100 mg. q.i.d. daily is recommended.

SUPPLIED: Tablets, 50 mg. and 100 mg. Oral Suspension, 25 mg. per 5 cc. tsp.

REFERENCES: 1. Birchall, R.: Am. Practit. *11*:918, 1960. 2. Jawetz, E., et al.: A.M.A. Arch. Intern. Med. *100*:549, 1957. 3. Lippman, R. W., et al.: J. Urol. *80*:77, 1958.

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EATON LABORATORIES, Division of The Norwich Pharmacal Company, NORWICH, NEW YORK

To cure or control infection throughout the urinary system at every age of life... at every stage of infection

Furadantin®

brand of nitrofurantoin



in Ob-Gyn practice: prevent bacterial insult to traumatized cervicovaginal tissue

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a safe, single agent with singular benefits

From a recent study reporting the lowered incidence of postoperative morbidity following the use of FURACIN Vaginal Suppositories in operative gynecology—"Certainly a single agent is to be preferred to a combination of agents, providing comparable results are obtained."*

Used before and after cervicovaginal surgery, delivery, radiation therapy and certain office procedures, FURACIN controls infection, hastens healing, reduces discharge, malodor and discomfort.

FURACIN VAGINAL SUPPOSITORIES: FURACIN 0.3% in a water-miscible base. Box of 12, each 2 Gm. suppository hermetically sealed in yellow foil.

FURACIN CREAM: FURACIN 0.2% in a water-miscible cream base. Tube of 3 oz. with plastic plunger-type applicator.

*Grimes, H. G., and Geiger, C. J.: Am. J. Obst. & Gynec. 79:441, 1960.

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in monilial vaginitis

start therapy with the true specific

gentia-jel®

it works when others fail



- QUICKER CURES AND LESS RECURRENCES
- FAST RELIEF OF VULVAR ITCHING AND BURNING
- SPECIAL DISPOSABLE APPLICATORS PREVENT REINFECTION

WESTWOOD PHARMACEUTICALS • BUFFALO 13, NEW YORK

In Monilial Vaginitis why wait until other therapies fail... start your patients with gentia-jel



CURES ARE QUICKER . . . RECURRENCES LESS. Gentia-jel's unsurpassed monilia-killing power results in quicker cures and less recurrences. Gentia-jel contains gentian violet, the most effective agent known for the destruction of Monilia albicans. Its remarkable effectiveness is proved by its high rate of cures during the last trimester of pregnancy when vaginal mycotic infections are most difficult to cure.

FAST, GRATIFYING RELIEF OF VULVAR ITCHING AND BURNING. This soothing jel provides fast relief of vulvar itching and burning. This all important relief is often much faster than that provided by solid dosage forms such as tablets and suppositories.

DISPERSES AND PENETRATES INTO ALL FOLDS. Gentia-jel disperses completely over vaginal and cervical mucosa, penetrates into all folds and bathes the vulvar labia to destroy fungi and bacteria.

SPECIAL DISPOSABLE APPLICATORS PREVENT REINFECTION. Gentia-jel's applicators, unlike many, are never reused, they are discarded . . . eliminating a major cause of reinfection. The disposable applicators are more esthetic to the patient . . . and greatly appreciated.

EASIER FOR YOUR PATIENTS TO USE. (1) At bedtime, patient lies back with knees flexed, inserts applicator and instills Gentia-jel. (2) Applicator is removed and discarded and a vaginal tampon or pledget of cotton is inserted in the introitus. A sanitary pad should be worn.

YOUR PRESCRIPTION SHOULD BE FOR TWELVE. Treatment should be continued over 12 days to assure a negative smear.

Gentia-jel is supplied in packages of 12 single-dose disposable applicators. Contains: gentian violet 0.1%; lactic acid 3%; acetic acid 1.0%; in a water-soluble polyethylene glycol base.

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the true specific for monilial vaginitis

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WESTWOOD PHARMACEUTICALS • BUFFALO 13, NEW YORK



The Pregnant

and her need for milk's calcium and phosphorus –without excessive fat calories

Drinking enough milk during pregnancy to assure sufficient calcium has posed the problem of unwanted fat calories.

Now there's an easy, *natural* way to help assure her good calcium and nutritional status. Carnation Instant Nonfat Dry Milk provides *all* the calcium, protein, phosphorus and B-vitamins of fresh whole milk *with less than half the calories.*

For 25% more of these needed nutrients: Carnation Instant can be mixed over-strength by adding ⅓ cup extra crystals per quart. Less than 105 calories an 8-ounce glass, this enriched nonfat milk is one-fourth richer in calcium, protein, phosphorus and B-vitamins than ordinary nonfat milk. It tastes delicious, with a richer flavor she'll enjoy. Even mixed over-strength, it costs her only 12¢ a quart.



WRITE FOR CARNATION'S "DIET DURING PREGNANCY" — CARNATION COMPANY, LOS ANGELES 19, CALIFORNIA

THE CASE AGAINST CATHETERS & ENEMAS



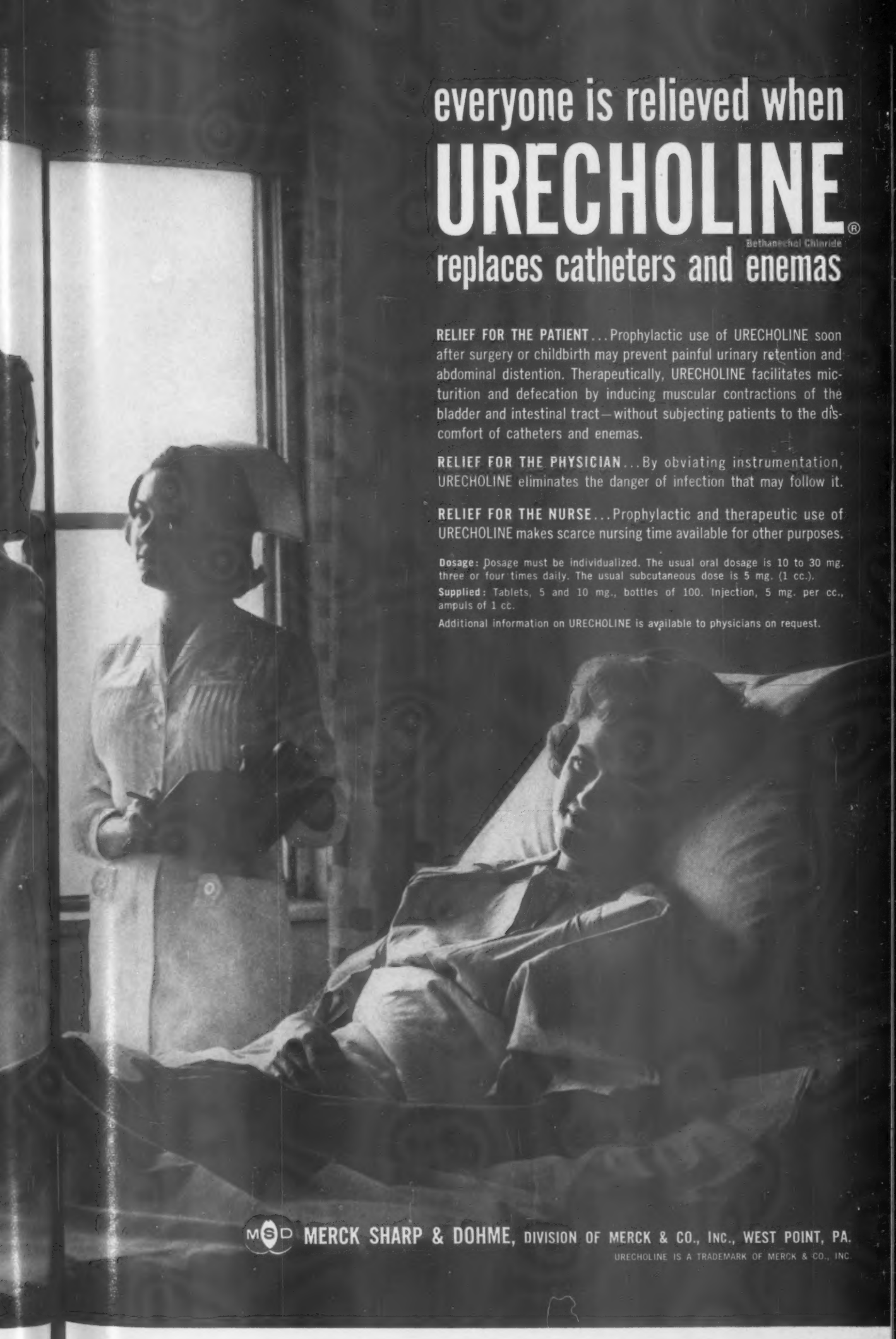
Catheters and enemas may be highly useful postoperatively and postpartum, but they are capable of serious drawbacks.

PATIENTS often dislike and fear such instrumentation, sometimes even more than the surgery or delivery that preceded it.

PHYSICIANS are mindful of the frequent risk of infection following catheterization, despite the most painstaking techniques. The passage of a sterile catheter into the bladder may introduce pathogens, since the urethra is not always sterile nor can it be readily sterilized.

NURSES find that catheterization and the administration of enemas require considerable time, which might be advantageously employed for other nursing procedures.





everyone is relieved when URECHOLINE®

Bethanechol Chloride

replaces catheters and enemas

RELIEF FOR THE PATIENT... Prophylactic use of URECHOLINE soon after surgery or childbirth may prevent painful urinary retention and abdominal distention. Therapeutically, URECHOLINE facilitates micturition and defecation by inducing muscular contractions of the bladder and intestinal tract—without subjecting patients to the discomfort of catheters and enemas.

RELIEF FOR THE PHYSICIAN... By obviating instrumentation, URECHOLINE eliminates the danger of infection that may follow it.

RELIEF FOR THE NURSE... Prophylactic and therapeutic use of URECHOLINE makes scarce nursing time available for other purposes.

Dosage: Dosage must be individualized. The usual oral dosage is 10 to 30 mg. three or four times daily. The usual subcutaneous dose is 5 mg. (1 cc.).

Supplied: Tablets, 5 and 10 mg., bottles of 100. Injection, 5 mg. per cc., ampuls of 1 cc.

Additional information on URECHOLINE is available to physicians on request.

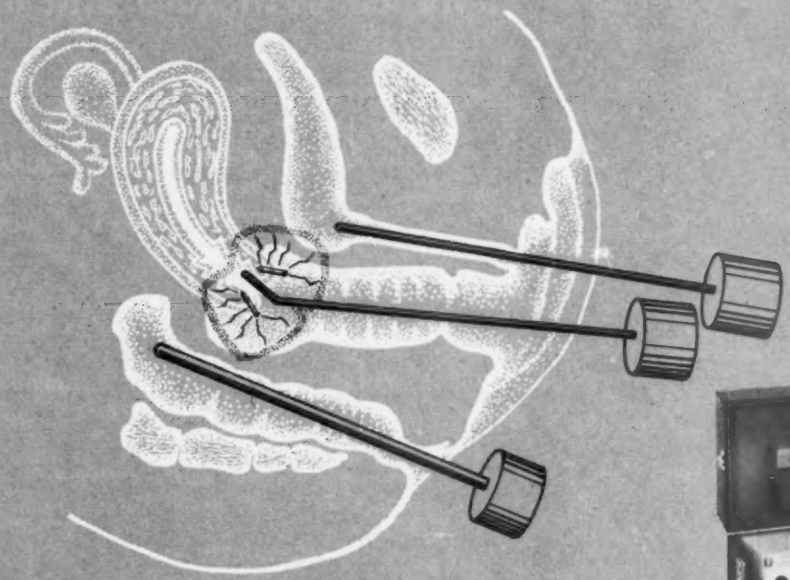
MSD MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., WEST POINT, PA.

URECHOLINE IS A TRADEMARK OF MERCK & CO., INC.

NEW

roentgen probitron

measures ACTUAL intracavitary radiation intensities





Curtis Nuclear's Model RA-400 Roentgen Probitron Assembly is used to measure intensity of radiation from implants inside the rectum, bladder and vagina. Featuring Continuous Sensitivity and Background Suppress Controls, the new instrument, complete with Detector and Probe, obsoletes mathematical computations in radiation measurements.

Inexpensive and unusually versatile, the Model RA-400 Roentgen Probitron Assembly takes into account differences in human dimensions, scatter and tissue absorption. It resolves small differences in space, utilizing unique radiation measuring concepts. Calibration is simple and reliable. Following calibration, the large panel meter indicates R/hr. For making permanent records, a recorder output is provided.

The Complete Model RA-400 Roentgen Probitron Assembly includes:

- **RR-402 Probitron Ratemeter**
- **P-11 Detector**
- **PR-16 (¼" dia.) Probe**
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- **CC-99 Carrying Case**

Price is $1,095.00 ..... F.O.B. Gardena, Calif.
The PR-26 ⅛" dia. (Straight) Probe $135.00
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Complete Accessories available for thyroid uptake and other standard radioisotope studies.

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facilitates management all through labor

reduces need for CNS depressants
In the early stages of labor, LARGON in combination with reduced doses of meperidine relieves the pain-tension cycle and controls nausea and vomiting. In definitely established labor, LARGON smooths induction of anesthesia and reduces requirements for narcotics and analgesics.

acts rapidly and predictably
Rapid action permits prompt evaluation of patient's status after administration. Duration of action parallels meperidine's and permits repeat doses without overlapping effect.

high order of safety
LARGON has not been observed to cause maternal or fetal depression, jaundice, blood dyscrasias, or adverse cardiovascular effects.

references: 1. Myers, J.D., et al.: Scientific Exhibit, A.M.A. Clinical Meeting, Washington, D.C., Nov. 29-Dec. 2, 1960. 2. Case reports on file, Medical Department, Wyeth Laboratories. 3. Glisson, C. S., and Pratt, C.: Bull. Fulton County Med. Soc. *35*:17 (June 1) 1961.

Wyeth Laboratories Philadelphia 1, Pa.

For further information on prescribing and administering LARGON, consult current Direction Circular enclosed with medication, or available on request.

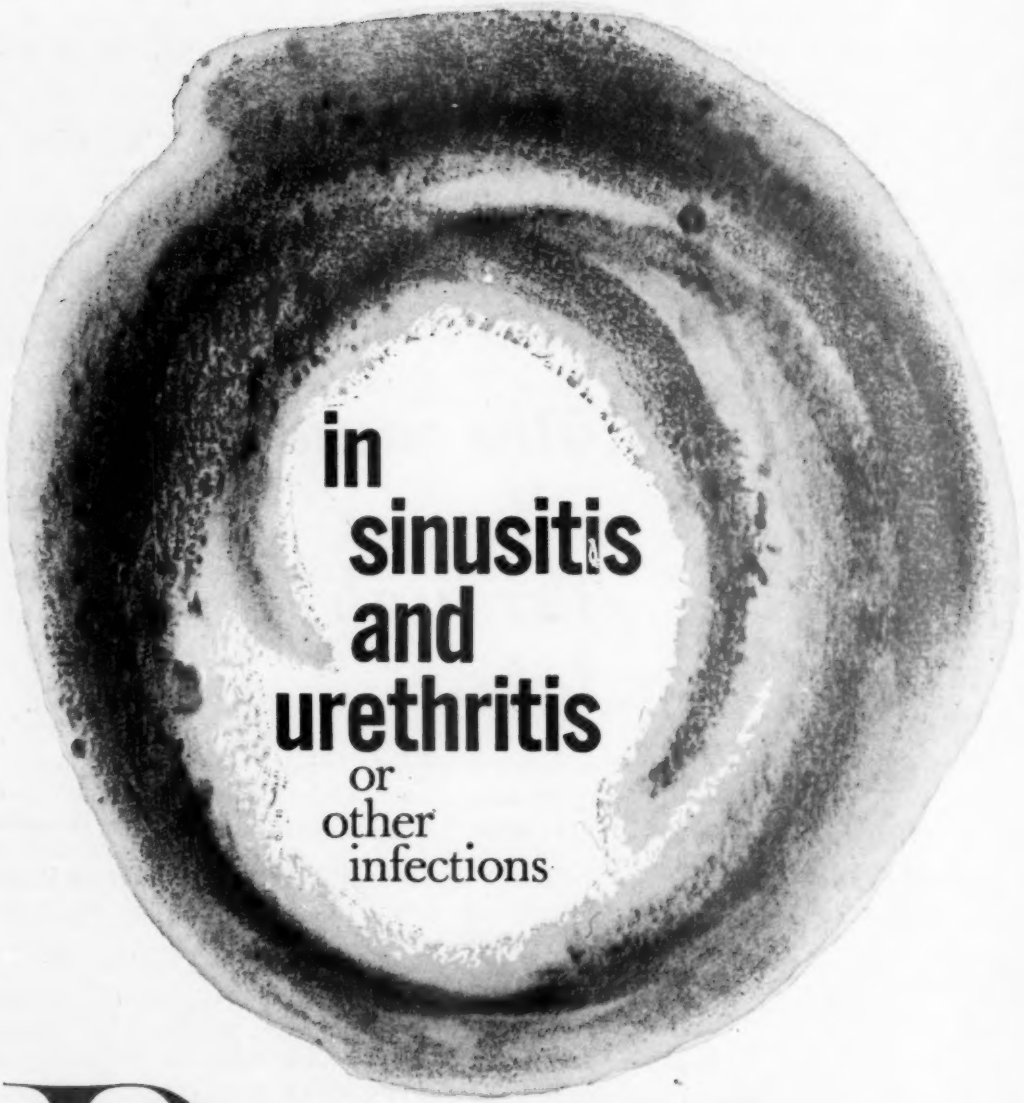
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antibiotic therapy with an added measure of protection

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DEMETHYLCHLORTETRACYCLINE LEDERLE

against relapse—up to 6 days' activity on 4 days' dosage
against secondary infection—sustained high activity levels
against "problem" pathogens—positive broad-spectrum antibiosis

CAPSULES, 150 mg., 75 mg.; PEDIATRIC DROPS, 60 mg./cc.; SYRUP, 75 mg./5 cc.

Request complete information on indications, dosage, precautions and contraindications from your Lederle representative or write to Medical Advisory Department.

LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

UNLIKE OTHER DISPOSABLE ENEMAS:

THOUGHTFUL TRAVAD® DESIGN CONSIDERS THE PATIENT—

PERMITS CONVENIENT SELF-ADMINISTRATION IN THE SITTING POSITION

TRAVAD simplifies the enema procedure—18 inches of permanently attached flexible tubing allows easier self-administration in any conventional position.

The time proven TRAVAD formula* cleans thoroughly and consistently. In fact, a single TRAVAD unit is more effective than *two*, one quart tap water enemas. Yet the small volume of fluid (135 cc.) does not cause distention, cramps or hyperactive evacuation. TRAVAD can be administered, retained and evacuated in about 10 minutes.[1]

To facilitate self-administration, the TRAVAD unit provides a safety guard on the prelubricated rectal tip and an infallible bead valve to prevent spillage or premature flow of enema solution.

Convenient TRAVAD is always ready to use, highly effective, and considerate of your patients. When ordering an enema for pre-examination or therapeutically, recommend TRAVAD.

(ready-to-use, disposable)

1. Weinstein, J.J.: unpublished manuscript.

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TRAVAD®/A SELF-ADMINISTERED ENEMA



*Each 100 ml. contains:
Sodium Dihydrogen Phosphate, 12 Gm. and Sodium Citrate, 10 Gm.
Preservatives: 0.1% Methylparaben 0.01% Propylparaben.

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POLYTHIAZIDE

1 mg. 2 mg. 4 mg.

A MORE CLINICALLY USEFUL
DIURETIC/ANTIHYPERTENSIVE

active antihypertensive
broad benefit
clinically confirmed
convenient control
dosage dexterity
dependable diuresis
enhanced effectiveness
foremost flexibility
increased individualization
long lasting
marked micturition
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orally optimal
peak potency
prolonged performance
reliable response
significant saluresis
tested toleration
unsurpassed utility
valuable versatility

"enhanced effectiveness" – In a 24-hour dose response study, RENESE produced a greater increase in sodium excretion than has been shown with four other currently available thiazides. In a controlled study[1] of patients with hypertensive cardiovascular disease, free of detectable edema, the 24-hour urinary volume increased by an average of 1.8 liters with an accompanying average weight reduction of 1.4 Kg. following a single 8 mg. dose of RENESE. The enhanced effectiveness of RENESE may produce response where previous therapy has failed or improve the response to present therapy.

1. Ford, R. V.: Current Therap. Res. 3:320, July, 1961

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For product information turn to page 80

THE BENEFITS OF SUSTAINED RELEASE IRON PLUS A FECAL SOFTENER



NEW FERRO-SEQUELS®

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TO MEET THE SPECIAL NEEDS OF PREGNANCY

A rational approach to the increased iron needs and increased G.I. sensitivity of pregnant patients. Sustained timed action releases iron in the area of optimal uptake—primarily in the duodenum-jejunum, and some in the ileum. The possibility of G.I. irritation is reduced because ferrous fumarate is a better tolerated form of iron, and because the concentration of iron is never unduly high at any point. FERRO-SEQUELS also contain dioctyl sodium sulfosuccinate which helps soften stools for easier elimination.

Each two-tone, green FERRO-SEQUELS contains:

Ferrous fumarate (equivalent to 50 mg. elemental iron)	150 mg.
Dioctyl sodium sulfosuccinate	100 mg.

Dosage: 1 or 2 SEQUELS daily. Supplied: Bottle of 30.

LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York



Roll and Waller have reported on the use of these suppositories following transurethral resection in 35 patients; 30 were followed from one to six months. Excellent results were obtained, with rapid relief of symptoms, freedom from side effects and no development of urethral strictures.

"We feel the good results are due to three functions performed by the suppositories. First of all, they mechanically dilate the urethra and cover the raw mucosal surfaces. Secondly, they combat infection and thus inflammation. Thirdly, the hydrocortisone directly suppresses inflammation and subsequent fibrosis."[1]

FURACIN-HC Urethral Suppositories combine the potent antibacterial action of FURACIN with the anti-inflammatory effect of hydrocortisone and prompt local anesthetic action of diperodon—plus gentle dilation.

Prevention of urethral strictures: postinstrumentation as in transurethral resection; postcatheterization ■ treatment of urethral strictures ■ treatment of urethral inflammation primary and secondary to infection and trauma ■ treatment of posterior urethritis and trigonitis in women

FURACIN-HC Urethral Suppositories—Box of 12, 1.3 Gm. each, hermetically sealed in aluminum foil. Each suppository contains FURACIN (brand of nitrofurazone) 0.2%, hydrocortisone acetate 1% and diperodon hydrochloride 2% in a water-dispersible base.

1. Roll, W. A., and Waller, J. I.: J. Urol., Balt. 81:289, 1959.

EATON LABORATORIES, Division of The Norwich Pharmacal Company, NORWICH, NEW YORK

Dulcolax®

brand of bisacodyl tablets and suppositories

the laxative with a bibliography

Geigy



The extensive bibliography* on Dulcolax, amounting to almost 100 clinical reports, strongly affirms its clinical advantages.

Induces Natural Evacuation
The action of Dulcolax is based on simple reflex production of large bowel peristalsis on contact with the colonic mucosa. As a result, stools are usually soft and well formed and purgation is avoided.

Predictable Action
With Dulcolax tablets action is almost invariably obtained overnight... with suppositories action occurs within the hour.

Wide Application
Dulcolax is as well adapted to preparation for radiographic and operative procedures as it is to the treatment of constipation.

*Detailed literature, including complete bibliography, available on request.

Dulcolax®, brand of bisacodyl: Tablets of 5 mg. and suppositories of 10 mg. Under license from C. H. Boehringer Sohn, Ingelheim.

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The Clinical Study:[1]

38 patients, male and female, all of whom gained weight on a previous diet regimen.

The Rx:

Desoxyn Gradumet, 10 or 15 mg., *once daily*, in the morning.

The Clinical Result:

The entire group averaged a weight loss of 15 pounds between two and 12 months of treatment. Eight women, weighing between 178 and 269 pounds, took Desoxyn for six months. They averaged a loss of 34 pounds. The heaviest woman lost 57 pounds, while another lost 71 pounds.

All the results weren't good, of course. One male actually gained seven pounds after four months. And there were two other patients whose weight remained unchanged after four and six months of treatment.

A Sidelight:

The clinician noted that there was an occasional finding of tablets in stools. He wrote: "A certain doubt existed in our minds that this residual tablet did not contain amphetamine. We arranged



for analysis for four of such tablets in patients taking 15 mg. and found that in each instance, there was no trace of amphetamine."

The Conclusion:

"Desoxyn has the best patient acceptance of any of the medications we have used as an appetite suppressant . . . It is our impression that Desoxyn Gradumet does slowly release amphetamine and thus, reduce side effects that are a problem. It is likewise our impression that the medication is a definite aid in weight reduction and has a high patient acceptability. We are at present using this drug in our practice as a routine adjutant to a weight reduction program."

1. Cole, R. E., Communication to Medical Department, Abbott Laboratories, 1961.

The Drug:

DESOXYN Gradumet®

(Methamphetamine Hydrochloride in Long-Release Dose Form*)

All-Day Appetite Control from a Single Oral Dose—5, 10 or 15 mg.

ABBOTT

*U.S. PAT. NO. 2,587,445 110242

when the need
for iron is acute...

inject

ASTRAFER® I.V.

(Brand of dextriferron)

intravenously

Write for literature and professional sample

ASTRA PHARMACEUTICAL PRODUCTS, INC.
Worcester, Mass., U. S. A.



OB11.

when hemorrhoids complicate pregnancy...

ANORECTAL COMFORT IN MINUTES

start treatment with

ANUSOL-HC® hemorrhoidal suppositories with hydrocortisone acetate, 10 mg.

to reduce the inflammatory reaction and to provide immediate relief of anorectal pain and itching, two Anusol-HC Suppositories daily for 3 to 6 days.

then to maintain patient comfort

ANUSOL® suppositories and unguent

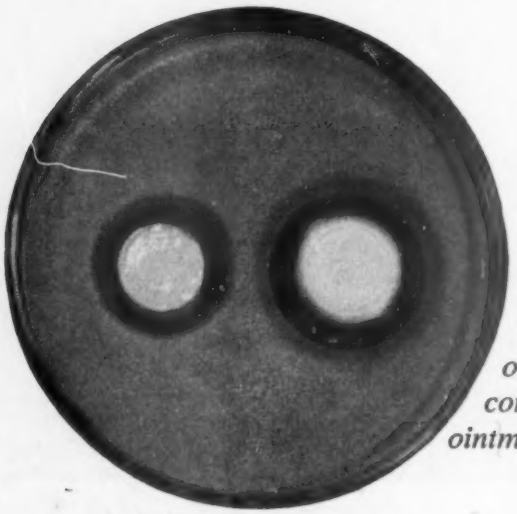
to prevent recurrence of symptoms, one Anusol Suppository morning and evening and after each evacuation. Supplement with Anusol Unguent as required.

Neither Anusol nor Anusol-HC contains analgesic or anesthetic drugs which might mask symptoms of serious rectal pathology.

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If 2 ointments contain the same antibiotics, how can one be more effective?

...The unique base* of Neo-Polycin releases a greater concentration of antibiotic into the lesions.



Neo-Polycin Ointment on right conventional grease-base ointment on left

Agar incubations show Neo-Polycin® Ointment more effective against common topical pathogens

This agar plate, containing *Staph. aureus*, was incubated for 24 hours at room temperature. Note the greater zone of inhibition around Neo-Polycin Ointment (right), than around the grease-base ointment of comparable antibiotic content (left). Tests on the following pathogens gave similar results: *beta hemolytic strep., E. coli, Proteus vulgaris, Pseudomonas aeruginosa.* Higher concentrations of antibiotics released from Neo-Polycin tend to inhibit the growth of relatively resistant strains and minimize antibacterial resistance created by sub-effective concentrations.

formula: Each gram of Neo-Polycin Ointment contains 4.28 mg. neomycin sulfate (3 mg. neomycin base), 400 units zinc bacitracin, 8000 units polymyxin B sulfate.

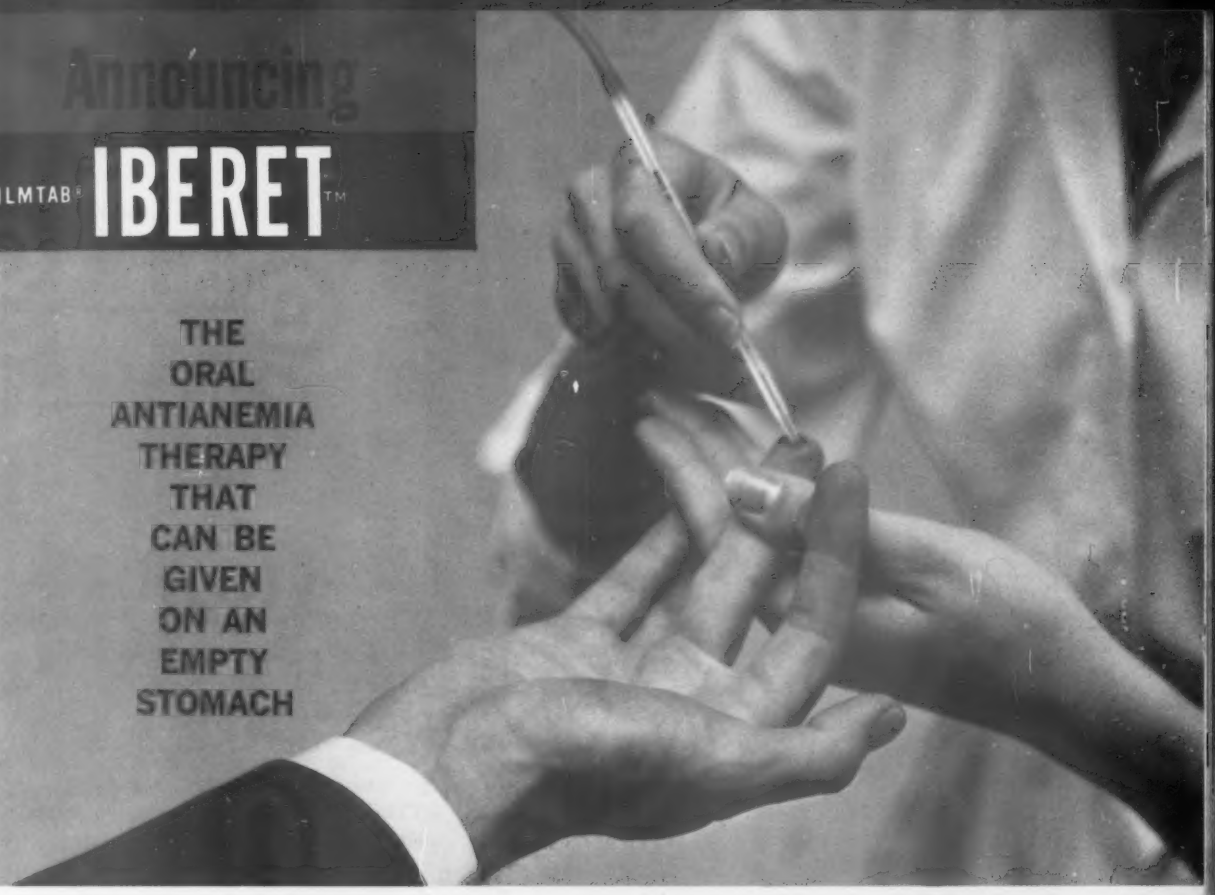
*FUZENE®—a patented base which is miscible with blood, pus, tissue exudates.

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Announcing

FILMTAB® IBERET™

THE ORAL ANTIANEMIA THERAPY THAT CAN BE GIVEN ON AN EMPTY STOMACH



Delivers 88% of its controlled release iron after the first half-hour
Result: less iron in the stomach, less gastric irritation

In view of the multiple factors which can adversely affect iron absorption, it has been stated that, ". . . therapeutic iron should be given on an empty stomach."[1] But, in the past, this meant a greater incidence of side effects such as nausea, abdominal pain, diarrhea or constipation, and even heartburn.

Iberet solves this problem by a smoothly controlled release of the major portion of its iron content *after* it leaves the stomach. Maximal release occurs where it can do the most good—in the intestinal tract—reducing the incidence and severity of gastrointestinal upset without impairing the therapeutic efficacy. *Iberet is exclusively formulated with the Ferrous Sulfate in Gradumet form so that it can be given on an empty stomach.*

The importance of the B-complex[2] and ascorbic acid to all cellular metabolic functions has been pointed out.[3] For this reason, therapeutic B-complex plus vitamin C are added to the Iberet formula to obtain maximal hematopoiesis in the shortest possible time.



In this half, 525 mg. of ferrous sulfate are provided in the ingenious Gradumet vehicle—engineered to deliver maximum release after the tablet is out of the stomach.

Here, to help insure maximal hematopoiesis, is therapeutic B-complex plus 150 mg. of vitamin C.

Just *one* Iberet Filmtab® a day supplies potent antianemia therapy—provides approximately the same hemoglobin response as ferrous sulfate given two or three times a day. Give Iberet at any time of day or night, even on an empty stomach. Iberet delivers most of its iron when and where it's best used—in the intestine.

JUST ONE DOSE DAILY PROVIDES:

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*Ferrous Sulfate, U.S.P. (Elemental Iron—105 mg.)	525 mg.

Plus Therapeutic B-Complex

Cobalamin (Vitamin B_{12})	25 mcg.
Thiamine Mononitrate	6 mg.
Riboflavin	6 mg.
Nicotinamide	30 mg.
Pyridoxine Hydrochloride	5 mg.
Calcium Pantothenate	10 mg.

Plus Vitamin C

Ascorbic Acid	150 mg.

Note: Filmtab® Fero-Gradumet™ with 105 mg. of Elemental Iron only, in long-release dose form, is also available.

[1]Woodruff, C.W., "Iron"; Borden's Review of Nutrition Research, 20:61, 1959.
[2]Vilter, R.W., "Essential Nutrients in the Management of Hematopoietic Disorders of Human Beings"; Am. J. Clin. Nutrition, 3-72, 1955.
[3]Brown, M.J., "Nutritional Problems in Surgery"; Surg. Clin. North America, 34-1239, 1954.

*In controlled-release dose form.
Filmtab—Film-sealed tablets, Abbott: U.S. Patent No. 2,881,085.
Iberet—Vitamin B-Complex, Vitamin C, and Controlled-Released Iron, Abbott.
Fero-Gradumet—Ferrous Sulfate in Controlled-Release Dose Form, Abbott.
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(prenatal vitamin-mineral supplements, Lilly)



One-Pulvule®-a-day convenience and economy
A single Pulvule daily provides comprehensive vitamin-mineral supplementation throughout pregnancy and lactation.

Concentrated nutritional support
En-Cebrin provides phosphorus-free calcium plus important vitamins and minerals.

Invitingly styled
The pink-and-blue En-Cebrin Pulvules are supplied in decorative bottles to enlist patient co-operation.

Each Pulvule provides:	
Vitamin A Synthetic (4,000 units)	1.2 mg.
Thiamine Mononitrate (B_1)	3 mg.
Riboflavin (B_2)	2 mg.
Nicotinamide	10 mg.
Pyridoxine Hydrochloride (B_6)	2 mg.
Vitamin B_{12} (Activity Equivalent)*	5 mcg.
Calcium Pantothenate (as Calcium Pantothenate, Racemic)	5 mg.
Ascorbic Acid (C)	50 mg.
Vitamin D Synthetic (400 units)	10 mcg.
Rutin	10 mg.
Calcium Carbonate (Equivalent to Calcium, 250 mg.)	625 mg.
Ferrous Fumarate (Equivalent to Iron, Elemental, 30 mg.)	90 mg.
Iodine (as Potassium Iodide)	0.15 mg.
Copper (as the Sulfate)	1 mg.
Magnesium (as the Oxide)	5 mg.
Manganese (as the Glycerophosphate)	1 mg.
Zinc (as the Chloride)	1.5 mg.

*Obtained from extractives of suitable microbial organisms and determined microbiologically against vitamin B_{12} standard.

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En-Cebrin® F (prenatal vitamin-mineral supplements with folic acid, Lilly)

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Dramamine®
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For dizziness/vertigo in older patients
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a more clinically useful diuretic/antihypertensive

IN BRIEF

RENESE (polythiazide) is a new, highly potent, orally effective, nonmercurial diuretic, saluretic, and antihypertensive agent with a high therapeutic index, low order of toxicity, and an intrinsically prolonged duration of action which enhances the excretion of sodium and chloride by the renal tubules.

INDICATIONS: RENESE is indicated for the treatment of hyper+ension and edema. It has been found useful in congestive heart failure, fluid retention of pregnancy, premenstrual tension, obesity (where fluid retention is present), renal edema, cirrhosis, drug-induced edema, and toxemia of pregnancy.

ADMINISTRATION AND DOSAGE: *Initial dose:* Depending on the severity of the conditions, initial doses of RENESE may range from 1 mg. to 4 mg. daily (refractory cases may require as much as 12 mg. daily). *Maintenance dose:* Usual effective maintenance doses range from 1 mg. to 4 mg. daily, depending on the severity of the cases. Some patients have responded to 1 mg. every other day (0.5 mg. daily).

SIDE EFFECTS AND PRECAUTIONS: Since all diuretic agents may reduce serum levels of sodium, chloride, and potassium, patients on RENESE should be observed regularly for early signs of fluid or electrolyte imbalance. Caution must be exercised during digitalis administration to prevent hypokalemia since patients are then more sensitive to the development of digitalis toxicity. During RENESE therapy of edema in patients with chronic renal disease, routine precautions should be taken against renal failure as indicated by an increasing blood urea nitrogen. Like other thiazide diuretics, RENESE may cause a rise in serum uric acid levels and should therefore be used with caution in patients with gout. Should overt manifestations of gout appear, the concomitant use of uricosuric agents may be effective in relieving the symptoms. Side effects with RENESE, such as nausea, vertigo, weakness, and fatigue are infrequent and seldom require cessation of therapy. Most of these reactions may be overcome by reducing the dose of RENESE or by taking measures to improve any electrolyte imbalance. Mild maculopapular skin rash has been rarely reported. Extra precautions may be necessary in patients who may require norepinephrine, or curare or its derivatives.

SUPPLIED: RENESE is available as 1 mg., white, scored tablets in bottles of 30; 2 mg., yellow, scored tablets in bottles of 30; 4 mg., white, scored tablets in bottles of 30.

More detailed professional information available on request.

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1 mg. 2 mg. 4 mg.

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DIURETIC/ANTIHYPERTENSIVE

active antihypertensive
broad benefit
clinically confirmed
convenient control
dosage dexterity
dependable diuresis
enhanced effectiveness
foremost flexibility
increased individualization
long lasting
marked micturition
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orally optimal
peak potency
prolonged performance
reliable response
significant saluresis
tested toleration
unsurpassed utility
valuable versatility

"dosage dexterity" – The sustained single-dose effectiveness of RENESE,[1] lasting at least 24 hours, permits flexibility of administration without diminished therapeutic efficacy. Available as 1 mg., 2 mg., and 4 mg. scored tablets, RENESE maintains most patients effectively and conveniently on once-a-day dosage.

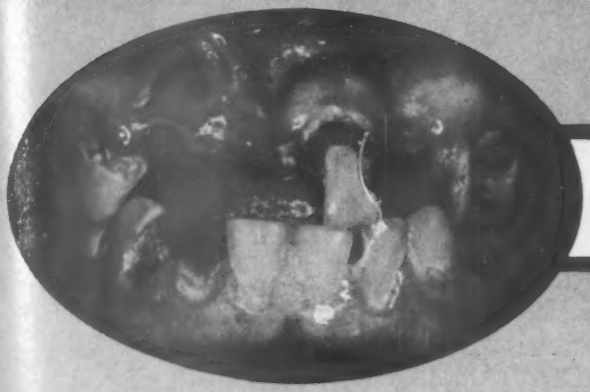
1. Ford, R. V.: Current Therap. Res. 3:320, July, 1961.

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"To achieve maximal caries-preventive effect, fluoride should be ingested during the time when the teeth are in the formative stage and throughout the caries-susceptible years. This ingestion must cover a period from the fourth month *in utero* (when the first deciduous central incisors begin to calcify) to the age of 18 years."

Report of Joint Committee of American Academy of Pediatrics and American Society of Dentistry for Children: Dental caries and a consideration of the role of diet in prevention, Pediatrics 23:400-407 (February) 1959;



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CONVENIENT ONE-TABLET-A-DAY DOSAGE

EACH CAPSULE-SHAPED TABLET CONTAINS: fluorine (from 2.21 mg. sodium fluoride) 1 mg., elemental iron (from 135 mg. ferrous sulfate exsiccated) 40 mg., calcium (from 625 mg. calcium carbonate) 250 mg., vitamin A 6000 USP units, vitamin D 400 USP units, vitamin B_1 1.3 mg., vitamin B_2 2 mg., vitamin B_6 3 mg., vitamin B_{12} 2 mcg., vitamin C 100 mg., niacinamide 20 mg., calcium pantothenate 5 mg.

USUAL ORAL DOSE: One tablet daily. Preferably during a meal.

AVAILABLE ON PRESCRIPTION ONLY
CONTRAINDICATED IN COMMUNITIES WITH FLUORIDATED DRINKING WATER.

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samples and literature — write Medical Department
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In a recent clinical study, the marked increase in pregnancy success rate demonstrates "the therapeutic superiority of Ethiodol hysterosalpingography over hysterosalpingography with other radiopaque media or carbon dioxide insufflation in the treatment of infertility."[2]

Ethiodol is preferred because..."It is an ideal radiopaque medium for hysterosalpingography. Because of its much lower viscosity it is preferable to... any other oily radiopaque medium. X-ray films with Ethiodol give... much better defined contrast than with any of the aqueous, acacia, or other water soluble media."[2]

Ethiodol® brand of ethiodized oil, is the ethyl ester of the iodized fatty acids of poppy seed oil, containing 37% iodine. It is available in 10 cc. ampules, boxes of two. A development of Guerbet Laboratories.

Bibliography: 1. Finegold, Wilfred J.: Internat. J. of Fertil. 3:143 1958
2. Palmer, A.: Internat. J. of Fertil. 4:365 1959



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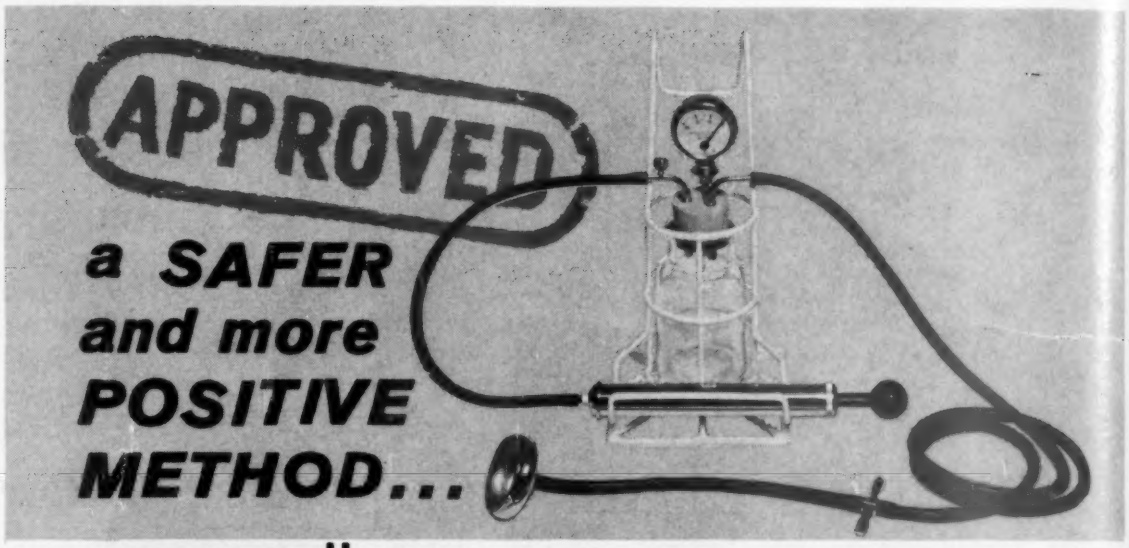
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"but why don't you tell my patients...?"

We pharmaceutical manufacturers, over the past several years and in various ways, have been trying to tell the story of the drug industry's role as a member of the American health team, and thus to correct certain unfortunate misconceptions. And all along we have looked upon you of the medical profession, on whose good will we are so dependent, as perhaps our chief audience.

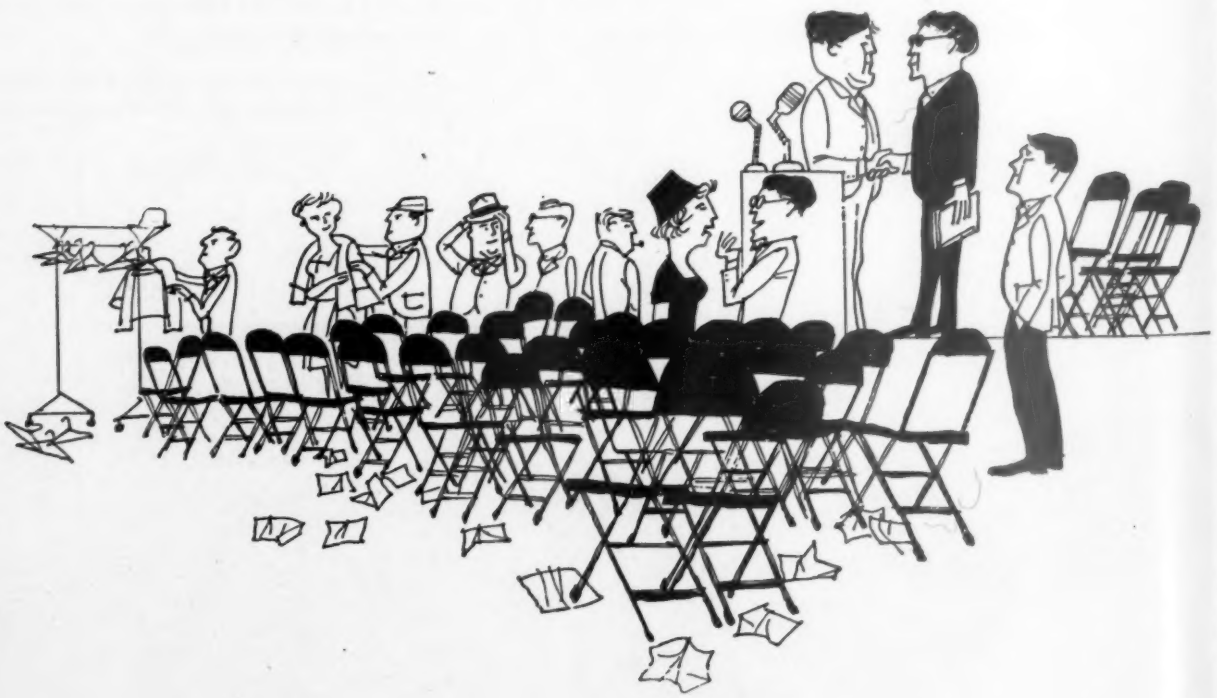
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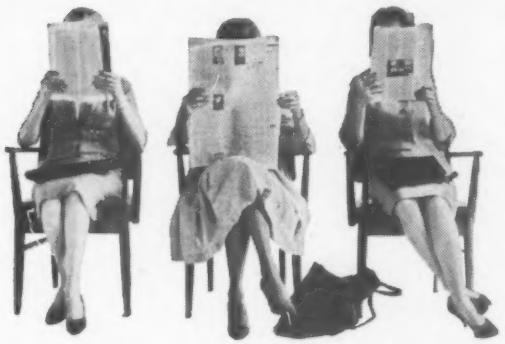
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chemically... 17-alpha-ethinyl-19-nortestosterone acetate—the acetate ester of norethindrone.

physiologically... an effective progestational agent—in this respect, exceeding not only oral ethisterone and parenterally administered progesterone but oral norethindrone as well.

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PARKE, DAVIS & COMPANY, Detroit 32, Michigan

PACKAGING: 5-mg. scored tablets, bottles of 30.
See medical brochure for details of administration and dosage.

*Kistner, R. W.: *Clin. Pharmacol. & Therap.* 1:525, 1960.

40561

INDICATION: *Episiotomy*



INDICATED:

Chymoral®

in over 2000 episiotomies Chymoral reduced undesirable inflammatory sequelae in 9 out of 10 patients

RESULTS WITH CHYMORAL AS OF JUNE 15, 1961[1]

	No. of Cases	Excellent	Good	Fair	No Response
Episiotomies	2,180	1,264	755	106	55
		← 97.5% →			← 2.5% →

Schmitz and Pavlic[2] evaluated CHYMORAL in episiorrhaphy in a controlled study of 500 obstetric patients. The 250 patients receiving CHYMORAL had a more rapid subsidence of edema and less pain than the 250 patients in the untreated (control) group. The CHYMORAL treated patients required less analgesia, fewer catheterizations and had less discomfort. ". . . none of the treated patients experienced side effects of any kind."[2]

1. Clinical Reports from the Medical Department, Armour Pharmaceutical Company, 1961. 2. Schmitz, H. E., and Pavlic, R. S.: Control of edema and pain in episiotomy. Use of oral proteolytic enzymes, Obst. & Gynec. *17*:260, 1961.

CHYMORAL

Chymoral is an ORAL anti-inflammatory enzyme tablet specifically formulated for intestinal absorption. Each tablet provides enzymatic activity, equivalent to 50,000 Armour Units, supplied by a purified concentrate which has specific trypsin and chymotrypsin activity in a ratio of approximately six to one. ACTION: Reduces inflammation of all types; reduces and prevents edema except that of cardiac or renal origin; hastens absorption of blood and lymph extravasates; helps to liquefy thick tenacious mucous secretions; improves regional circulation; promotes healing; reduces pain. INDICATIONS: Chymoral is indicated in respiratory conditions such as asthma, bronchitis, rhinitis, sinusitis; in accidental trauma to speed absorption of hematoma, bruises, and contusions; in inflammatory dermatoses to ameliorate acute inflammation in conjunction with standard therapies; in gynecologic conditions such as pelvic inflammatory disease and mastitis; in obstetrics as episiotomies and breast engorgement; in surgical procedures as biopsies, hernia repairs, hemorrhoidectomies, mammectomies, phlebitis and thrombophlebitis; in genitourinary disorders as epididymitis, orchitis and prostatitis; in dental and oral surgery as fractures of the mandible or maxilla, difficult or multiple extractions, and alveolectomies. CONTRAINDICATIONS: None known. INCOMPATIBILITIES: None known. Antibiotics as well as generally accepted measures may be coadministered. SIDE EFFECTS: Mild gastric upsets, rarely encountered. DOSAGE: Recommended initial dose is two tablets q.i.d.; one tablet q.i.d. for maintenance. SUPPLIED: Bottles of 48 and 250 tablets.

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Two Pyridium tablets t.i.d. relieve the pain of urinary infection in only 30 minutes. During the first 3 to 4 days of therapy, Pyridium, prescribed along with any antibacterial of your choice, will make your patient comfortable until the antibacterial reduces inflammation and controls the infection.

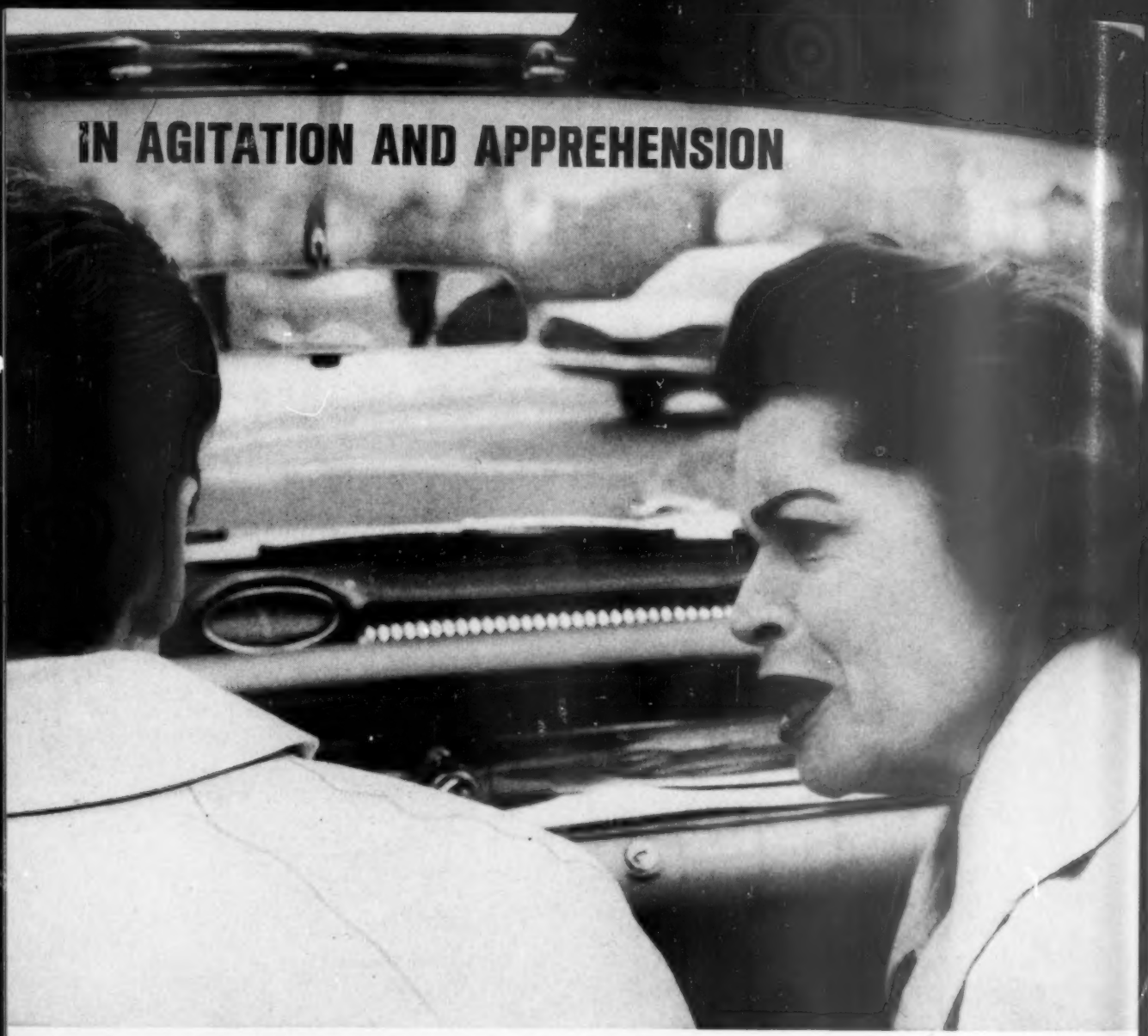
AVERAGE DOSE: Adults—2 tablets t.i.d. Children 9 to 12 —1 tablet t.i.d. SUPPLIED: 0.1 Gm. tablets, bottles of 50. PRECAUTIONS: Pyridium is contraindicated in patients with renal insufficiency and/or severe hepatitis. *Full dosage information, available on request, should be consulted before initiating therapy.*

WARNER CHILCOTT

MORRIS PLAINS, N.J.

9-12

Makers of TEDRAL GELUSIL PROLOID PERITRATE MANDELAMINE

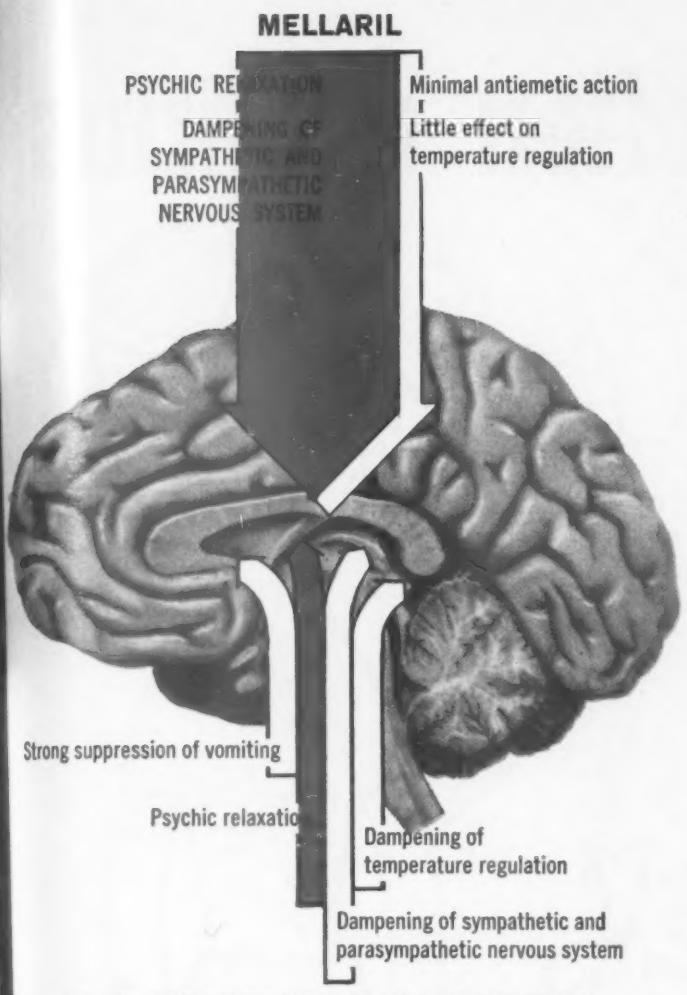


Mellaril®

THIORIDAZINE HCl

provides highly effective tranquilization, relieves agitation, apprehension, anxiety

"The literature is replete with references to the phenothiazines and the role they play in the treatment of tension states, anxiety, and agitation. While numerous compounds have been introduced, the search continues for an ataraxic that is not only effective, but is relatively free of annoying side effects. My experience with thioridazine [Mellaril] in 87 patients confirms the findings of other investigators regarding its efficacy in the control and treatment of various nervous and mental disturbances seen in everyday practice."[1]



OTHER PHENOTHIAZINE-TYPE TRANQUILIZERS

"The side-effects which we have observed during trials with Mellaril have not been of a serious nature and we believe that the claim can justly be made that Mellaril has fewer side-effects than any other of the phenothiazine compounds."[2]

greater specificity of tranquilizing action results in fewer side effects

1. Mellaril has a specificity of tranquilizing action on certain brain sites, in contrast to the more "diffuse" action of other phenothiazines. For example, unlike other phenothiazine tranquilizers, Mellaril provides tranquilization without any significant antiemetic action.
2. Mellaril has less "spill-over" action to other brain areas. Hence, such extrapyramidal effects as parkinsonism are rare.
3. Jaundice has not been observed.

Mellaril is indicated for agitation, apprehension and anxiety, ranging from mild to severe, in both ambulatory and hospitalized patients.

ADULT DOSAGE – Usual starting dose: Non-psychotic patients – 10 or 25 mg. t.i.d.; Psychotic patients – 100 mg. t.i.d. Dosage must be individually adjusted until optimal response. Maximum recommended dosage: 800 mg. daily.

CHILDREN'S DOSAGE – Average 10 mg. t.i.d. (range: 20 – 40 mg. per day).

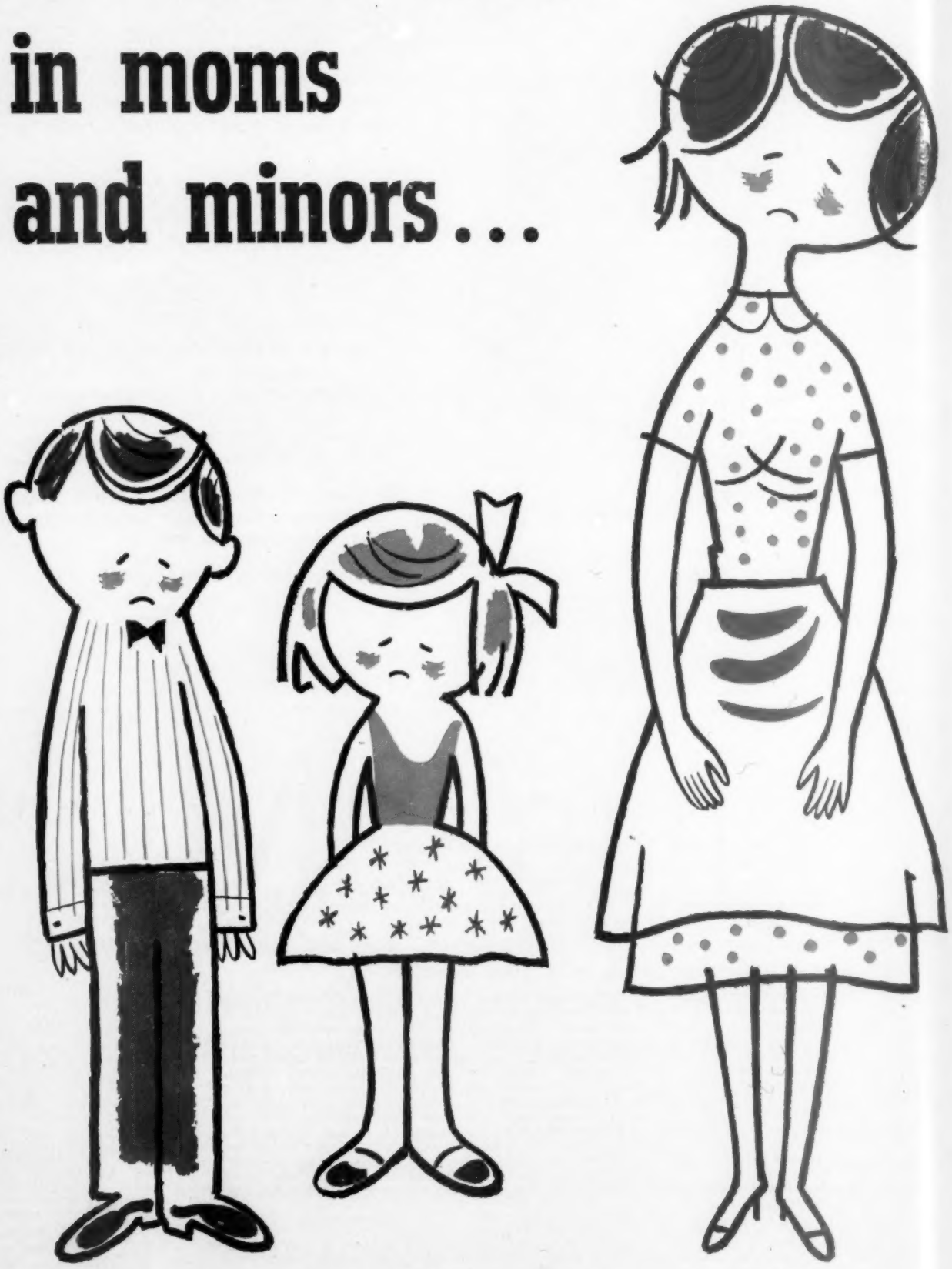
Supply: Mellaril Tablets, 10 mg., 25 mg., 50 mg., 100 mg., 200 mg.

PRECAUTIONS: Leukopenia and/or agranulocytosis, photosensitization and convulsive seizures have been reported with long-range therapy but are very rare. Jaundice has not been observed during the use of Mellaril. Pseudoparkinsonism and other extrapyramidal disorders may occur but are infrequent and mild. Pigmentary retinopathy, which has been observed in psychiatric patients taking large doses (in excess of 1600 mg. daily over long periods of time) is characterized by diminution of visual acuity, brownish coloring of vision, and impairment of night vision; examination of the fundus discloses deposits of pigment. The possibility of this complication is avoided by remaining within the recommended limits of dosage. Drowsiness is not infrequent, especially with large doses and during early treatment. Dryness of the mouth, nasal stuffiness, skin eruption, nocturnal confusion, galactorrhea and amenorrhea are noted occasionally. Some male patients have complained of inability to ejaculate. Female patients appear to have a greater tendency to orthostatic hypotension than male patients. As with other phenothiazines, Mellaril is contraindicated in severely depressed or comatose states from any cause.

1. Freed, S. C.: Thioridazine, a neuroleptic in general practice, International Record of Medicine, 172:644, Oct. 1959. 2. Sandison, R. A., Whitelaw, E., and Currie, J. D. C.: Clinical trials with Mellaril in the treatment of schizophrenia, Journal of Mental Science (British Journal of Psychiatry) 106:732, April 1960.

SANDOZ
ORIGINAL RESEARCH SERVING THE PHYSICIAN

IRON: often a minus in moms and minors...





LIVITAMIN®

. . . the hematinic with built-in nutritional support

Many growing children and most women of menstrual age deplete their iron reserves and slide into iron-deficiency anemia.

Livitamin changes the minus to a plus because it restores depleted iron reserves and also provides integrated nutritional support.

Iron in Livitamin is well absorbed, with minimum gastric upset and constipation. And with Livitamin there is no worry about teeth stain . . . or taste acceptance.

WRITE FOR LITERATURE
AND DOSAGE INFORMATION.

FORMULA: Each fluidounce contains:

Iron, peptonized (equiv. in elemental iron to 71 mg.)	420 mg.
Manganese citrate, soluble, N.F.	158 mg.
Thiamine hydrochloride	10 mg.
Riboflavin	10 mg.
Cobalamin	20 mcg.
Nicotinamide	50 mg.
Pyridoxine hydrochloride	1 mg.
Pantothenic acid	5 mg.
Liver fraction 1	1 Gm.
Rice bran extract, U.S.P. XIV	1 Gm.
Inositol	30 mg.
Choline	60 mg.

SUPPLIED: *Liquid:* 8 oz. bottles, pints, gallons; *Capsules:* Bottles of 100, 500, 1000. Also available as LIVITAMIN with INTRINSIC FACTOR: bottles of 100 capsules.

THE S. E. MASSENGILL COMPANY

Bristol, Tennessee • New York • Kansas City • San Francisco



GIVE HELP TO THE GOOD SHIP HOPE

In the troubled waters off Southeast Asia, a group of Magnificent Americans—doctors, dentists, nurses and various technicians—are waging the peace by training and teaching local medical workers to eventually meet their vast health problems.

To the Indonesian press, these Americans and this ship represent "the heart of a mighty nation." For information on how you can help the good ship HOPE, write to Project HOPE, 1818 M St., N.W., Washington 6, D. C.





in the treatment of vaginitis... physicians have asked...

Q How do TRIB SUPPOSITORIES and CREAM differ from other antivaginitis agents?

A Only TRIB preparations contain Triburon Chloride, the wide-spectrum *topical* microbicide which is effective in trichomonal, monilial and bacterial infections.

Q Why is this important for vaginal therapy?

A Since vaginal infections are rarely caused by single invading organisms, the broad-spectrum effectiveness of TRIB agents assures greater healing in more patients.

Q What distinct advantages do TRIB preparations have over broad-spectrum antibiotics and other microbicides?

A Though TRIB is effective against most commonly encountered vaginitides, including many antibiotic-resistant staph. and strep., resistant strains rarely develop in spite of prolonged use. Since Triburon Chloride is used only topically, there is no danger of sensitizing the patient to an antimicrobial which the physician may wish to use systemically.

Q How do TRIB preparations penetrate the vaginal rugae which often harbor pathogens?

A TRIB preparations are water-soluble and self-emulsifying, assuring a high rate of diffusion and prolonged retention.

Q What other TRIB properties promote healing?

A TRIB preparations approximate the pH of the normal healthy vaginal tract and are not irritating to the mucosa. Also, their many esthetic features encourage patient cooperation, even in prolonged usage.

ROCHE LABORATORIES Division of Hoffmann-La Roche Inc.

Trib™ Vaginal Suppositories and Cream

contains Triburon® Chloride 0.1%

consistent response in vaginal infections

controls vaginitis symptoms... attacks vaginitis causes...



- **RAPID SYMPTOMATIC RELIEF:** itching and burning usually disappear after only 1 or 2 **TRIB** applications.
- **EFFECTIVE IN ALL THREE:** trichomonal, monilial and nonspecific bacterial vaginitis respond to **TRIB** in up to 85% of cases.
- **NONSENSITIZING, NONIRRITATING:** no evidence of systemic or local reaction; **TRIB** is well tolerated in the vagina and on raw vulvar surfaces.
- **DEMONSTRATED SAFETY:** therapy with **TRIB** may safely be continued during pregnancy and menstruation without untoward reactions.

AND MOST IMPORTANT TO YOUR PATIENTS...

- **ESTHETICALLY ACCEPTABLE:** suppository and cream are smooth, white, odorless, nonstaining and can be conveniently administered with accompanying applicators.

Supplied: TRIB VAGINAL SUPPOSITORIES—Boxes of 24 with reusable applicator. **TRIB VAGINAL CREAM**—3-ounce tubes with 18 disposable applicators. Consult literature and dosage information, available on request, before prescribing.

TRIBURON® CHLORIDE — N,N'-bis[1-methyl-3-(2,2,6-trimethylcyclohexyl) propyll-N,N'-dimethyl-1,6-hexanediamine bis (methochloride)

ROCHE LABORATORIES Division of Hoffmann-La Roche Inc.

Trib™ **Vaginal Suppositories and Cream**

contains Triburon® Chloride 0.1%

consistent response in vaginal infections

No finer name in contraceptives



21 26 years successful use without a diaphragm

SINCE 1934

WHITTAKER LABORATORIES, INC., PEEKSKILL, NEW YORK



You give food and friendship with every $1 package you send to the world's hungry thru the CARE Food Crusade, New York

Uncomplicated... **Bonine®** *basic for "morning sickness"*

BRAND OF MECLIZINE HYDROCHLORIDE



•effectiveness and toleration a matter of record
•free from occurrence of diverse metabolic effects
•bedtime dosage provides up to 24 hours' protection

IN BRIEF BONINE (meclizine hydrochloride), an antinauseant-antiemetic compound with antihistaminic and anticholinergic properties, is especially valuable in the symptomatic relief of nausea and vomiting of pregnancy. Additional indications are motion sickness, radiation sickness, vertigo associated with Ménière's syndrome, labyrinthitis, fenestration procedures, vestibular dysfunction, and dizziness associated with cerebral arteriosclerosis.

ADMINISTRATION AND DOSAGE: For control of nausea and vomiting of pregnancy, a single dose of 25 to 50 mg. at bedtime is usually effective. For dosage schedules in other indications, see product brochure.

SIDE EFFECTS: The side effects reported in association with BONINE have been uncomplicated, mild and/or transient and consist of occasional drowsiness, dryness of the mouth, and blurred vision. There are no known contraindications to BONINE.

PRECAUTIONS: As with other antihistaminic compounds, the physician should inform patients of the need for caution in driving a car or when engaged in other activities requiring alertness.

SUPPLIED: BONINE Tablets, scored, tasteless, 25 mg. BONINE Chewing Tablets, mint-flavored, 25 mg.

More detailed professional information available on request.

GOOD MORNING

Science for the world's well-being® Pfizer **PFIZER LABORATORIES** Division, Chas. Pfizer & Co., Inc. New York 17, N.Y.



The Milibis® vaginal suppository is soft and pliant as a tampon. It offers proved therapeutic action* in an exceptional vehicle. The suppository is clean, odorless and non-staining. The course of treatment of vaginitis (trichomonal, bacterial and monilial) with Milibis is short —only 10 suppositories in most cases. Milibis® vaginal suppositories are supplied in boxes of 10 with applicator.

Winthrop LABORATORIES
New York 18, N. Y.

*97 per cent effective in a study of 564 cases;
94 per cent effective in a study of 510 cases.

Milibis (brand of glycobiarsol).



When there's a pram in her future, she'll need Pramilets® today

Comprehensive vitamin-mineral support with just 1 Filmtab® daily

No one's ever said that looking ahead isn't a wise idea. (Granted, in time to come, thought will have to be given to diaper laundering.) However, perhaps little mother-to-be *should* take first things first.

Between now and arrival day, for instance, there's probably nothing that'll take precedence over the sound diet you'll prescribe for her. And Pramilets—with its stepped-up formula—more than ever complements the established regimen.

What's in order? Calcium? She gets a generous allowance with Pramilets. Iron? Pramilets provide a solid 40 milligrams of elemental iron (ferrous fumarate — the kind that's best-tolerated). As for the balance of the improved Pramilets formula, among the significant nutrients, vitamins C, B_6 and B_{12} have all been increased.

Finally, some of Pramilets' patient-pleasing features: Convenient dosage — one a day, usually . . . a compact size tablet . . . and an attractive bottle for table or dresser.

Pramilets supplied in bottles of 100 and 1000 Filmtabs — and new 180-Filmtab Economy Bottle. Also available: Pramilets-F (Rx only) with Folic Acid.

109240

FILMTAB—FILM-SEALED TABLETS, ABBOTT; U.S. PAT. NO. 2,881,085.

ABBOTT

for an ideal
prepartum/preoperative state

Vistaril

PARENTERAL SOLUTION

a well-tolerated, **general-use** tranquilizer with specific antiemetic and narcotic-sparing qualities



VISTARIL prepartum . . .
allays apprehension and fear without impairing ability to cooperate during labor and delivery[1]

reduces narcotic requirements and incidence of narcotic-induced respiratory depression; helps control nausea and vomiting; shortens stay in recovery room[1,2]



VISTARIL preoperatively...
allays anxiety and fear without depression of vital functions[1,2]

permits substantial reduction in meperidine or other narcotics with rare incidence of hypotension, respiratory depression, or other untoward effects; relaxes skeletal muscle and smooths recovery; helps control emesis[1,2]

Science for the world's well-being®

Pfizer

PFIZER LABORATORIES
Division,
Chas. Pfizer & Co., Inc.
Brooklyn 6, New York

...and when administered postpartum or after surgery, VISTARIL maintains tranquility and helps control nausea and vomiting

References: 1. Benson, C., and Benson, R. C.: Scientific Exhibit, Illinois Acad. Gen. Practice, Sept., 1960.
2. Grady, R. W., and Rich, A. L.: Scientific Exhibit, Am. Soc. Anesth., New York, Oct. 4-7, 1960.

IN BRIEF

VISTARIL Parenteral Solution is hydroxyzine hydrochloride.

Used preoperatively and postpartum, VISTARIL controls anxiety and fear, helps prevent emesis and smooths recovery. By reducing narcotic requirements substantially, VISTARIL helps to avoid narcotic-induced respiratory depression and hypotension. VISTARIL's calming effect usually does not impair discrimination, and is accompanied by direct and secondary muscle relaxation. No toxicity has been reported with VISTARIL, and it has a remarkable record of freedom from adverse reactions.

INDICATIONS: In addition to pre- and postpartum and pre- and postoperative tension and emesis, VISTARIL is clinically effective in other anxiety and tension states, senility, anxiety associated with various disease states, alcoholism, certain functional arrhythmias, and pediatric behavior problems.

ADMINISTRATION AND DOSAGE: VISTARIL dosage varies with the state and response of each patient, rather than with weight, and should therefore be individualized by the physician for optimum results. The usual dosage in prepartum and preoperative sedation is 25-50 mg. I.M. or I.V. q. 4 h., p.r.n. Orally, up to 400 mg. per day in divided doses.

SIDE EFFECTS: Drowsiness may occur in some patients; if so, it is usually transitory, disappearing within a few days of continued therapy or upon reduction of dosage. Dryness of mouth may be encountered at higher doses.

PRECAUTIONS: The potentiating action of hydroxyzine should be taken into account when the drug is used in conjunction with central nervous system depressants. Do not exceed 1 cc. per minute I.V. Do not give over 100 mg. per dose I.V. Parenteral therapy is usually for 24-48 hours, except when, in the judgment of the physician, longer-term therapy by this route is desirable.

SUPPLIED: VISTARIL *Parenteral Solution* (hydroxyzine hydrochloride)—10 cc. vials, 25 mg. per cc.; 2 cc. ampules, 50 mg. per cc. VISTARIL *Capsules* (hydroxyzine pamoate)—25, 50, and 100 mg. VISTARIL *Oral Suspension* (hydroxyzine pamoate)—25 mg. per 5 cc. teaspoonful.

More detailed professional information available on request.

TO *SIMPLIFY AND ASSIST* PRENATAL MANAGEMENT

fosfree®

A PHOSPHOROUS-FREE PRENATAL SUPPLEMENT



fosfree®... provides a comprehensive formula of essential phosphorous-free calcium plus the vitamins and minerals necessary to assist in the prevention and relief of . . .

- leg cramps resulting from calcium deficiencies
- vitamin and mineral deficiencies
- nausea of the prenatal patient
- secondary anemias

Results are achieved without constipation. Systemic alkalosis, phosphorous deprivation and chloride depletion are avoided.

fosfree®...

SUPPLIED: Bottles of 100

DOSAGE: Four tablets daily (one tablet mid-morning, one tablet midafternoon, and two tablets at bedtime).

The suggested daily schedule provides:

Calcium Lactate	1000. mg
Calcium Gluconate	1000. mg
Calcium Carbonate	1200. mg
(Calcium	703. mg)
Vitamin D_2	600. USP units
Vitamin A Acetate	6000. USP units
Vitamin E (as mixed Tocopherols)	5.0 I.U.
Ascorbic Acid (Vitamin C)	150. mg
Menadione (Vitamin K)	1.0 mg
Pyridoxine HCl (Vitamin B_6)	10. mg
Thiamine Mononitrate (Vitamin B_1)	8.0 mg
Riboflavin (Vitamin B_2)	8.0 mg
Niacinamide (Vitamin B_3)	40. mg
d-Calcium Pantothenate (Vitamin B_5)	20. mg
Ferrous Gluconate	320. mg
(Iron	37. mg)
Vitamin B_{12} (crystalline, on resin)	10. mcgm
Copper (as Sulfate)	0.60 mg
Manganese (as Citrate soluble)	1.0 mg
Zinc (as Oxide)	0.32 mg
Potassium (as Chloride)	20. mg
Magnesium (as Carbonate)	10. mg

COMPLETE LITERATURE AND SAMPLES ON REQUEST

Mission Pharmacal Co.
SAN ANTONIO 6, TEXAS

in induction and stimulation of labor—method of choice

PITOCIN

"Intravenous PITOCIN may be used successfully in elective or indicated inductions of labor. It has a definite place in the stimulation of labor in the early part or later stages either in desultory preliminary labor, or in primary or secondary uterine inertia."*

PITOCIN (oxytocin injection, Parke-Davis) is supplied in 0.5-cc. (5-unit) ampoules, in boxes of 10 and in 1-cc. (10-unit) ampoules, in boxes of 10. Each cc. contains 10 international oxytocic units (U.S.P. units). See medical brochure for details of administration and dosage.

*Fields, H.; Greene, J. W., Jr., & Franklin, R. R.: *Obst. & Gynec.* **13**:353, 1959.

PARKE-DAVIS

72161 PARKE, DAVIS & COMPANY, Detroit 32, Michigan



during pregnancy and the postpartum period[1,2]



whenever stool softening is all that's needed for natural evacuation

COLACE®

Dioctyl sodium sulfosuccinate, Mead Johnson

achieves evacuation without laxative action

When constipation must be avoided and easy evacuation is desirable, especially during the first and last trimesters of pregnancy, Colace achieves natural, comfortable evacuation by stool-softening action alone.

During the postpartum period, too, in the presence of painful hemorrhoids or fissures in ano, therapy with Colace has proved particularly useful. It corrects constipation without peristaltic stimulation and eliminates the need for straining at stool.

supplied: Colace Capsules (50 mg. and 100 mg.), bottles of 30, 60, and 250. Colace Liquid (1% solution, 10 mg. per cc.), bottles of 30 cc., with plastic 'Safti-Dropper' calibrated for 1 cc. Colace Syrup (20 mg. per teaspoon), bottles of 8 fluid ounces.

references: (1) Antos, R. J.: Southwestern Med. *37*: 236-237 (April) 1956. (2) Schoenfeld, R. C.: Am. J. Obst. & Gynec. *74*:1114-1115 (Nov.) 1957. 395R61

Mead Johnson Laboratories

Symbol of service in medicine

new Renese®
POLYTHIAZIDE

1 mg. 2 mg. 4 mg.

A MORE CLINICALLY USEFUL
DIURETIC/ANTIHYPERTENSIVE

active antihypertensive
broad benefit
clinically confirmed
convenient control
dosage dexterity
dependable diuresis
enhanced effectiveness
foremost flexibility
increased individualization
long lasting
marked micturition
notable natruresis
orally optimal
peak potency
prolonged performance
reliable response
significant saluresis
tested toleration
unsurpassed utility
valuable versatility

"active antihypertensive" – RENESE is a highly effective antihypertensive agent when used alone or concomitantly with other agents such as rauwolfia or blocking agents. Excellent-to-good clinical response has been reported in 145 out of 180 patients with hypertension alone and in 109 out of 128 patients with hypertension and associated congestive heart failure. Some of these patients had been refractory to previous therapy.

Pfizer *Science for the world's well-being®*

PFIZER LABORATORIES Division,
Chas. Pfizer & Co., Inc. New York 17, New York

For product information turn to page 80

WHY ACID MANTLE?

A DISTINCT THERAPEUTIC ENTITY*
Restores and maintains skin's normal protective acidity—speeds natural healing and helps sensitive skin resist irritants and infection.

A NOTABLE VEHICLE
Special water-miscible, evaporable base assures better dispersion, greater concentration of active ingredients in contact with skin—increases response through its own therapeutic action.

*Supplied: in Creme and Lotion (pH 4.6)



in pruritus ani et vulvae...

LIDA-MANTLE-HC™ CREME

lidocaine† and hydrocortisone alcohol in ACID MANTLE

INTERRUPTS THE ITCH-SCRATCH CYCLE

Stop itching to end scratching to start healing with...

LIDA-MANTLE-HC containing: non-toxic, non-irritating, virtually non-sensitizing lidocaine—encourages healing by avoiding traumatic damage from scratching; **micro-dispersed hydrocortisone**—effectively and rapidly reduces inflammation, and **ACID MANTLE**—helps to restore skin's normal protective acidity.

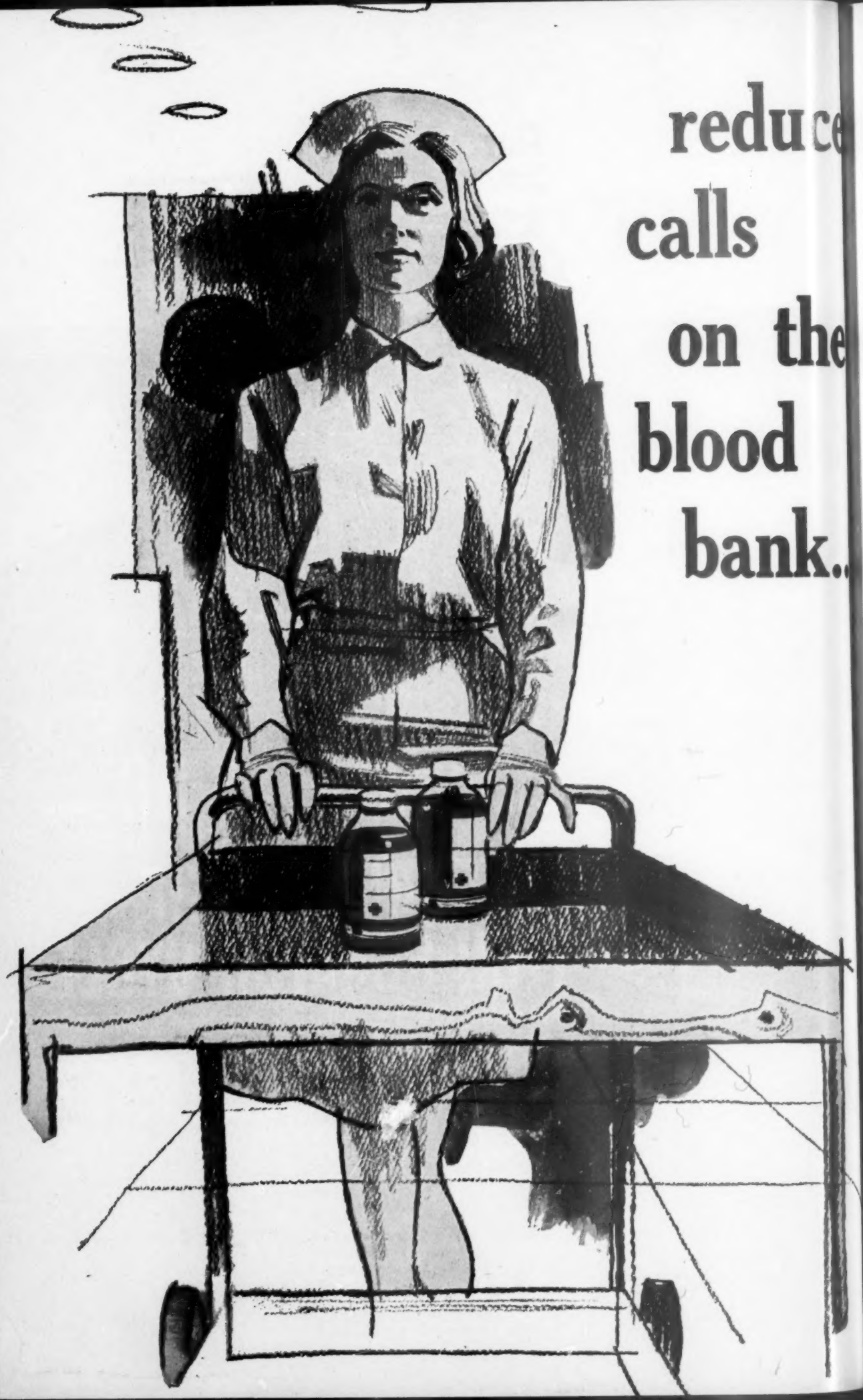
Available: LIDA-MANTLE-HC™ Creme in ½ oz. and 1 oz. tubes.

†XYLOCAINE, REG. TM., ASTRA PHARM. PROD., INC.
U.S. PAT. 2,441,498 (BRAND OF LIDOCAINE)

01461

WORLD LEADER IN DERMATOLOGICALS

DOME CHEMICALS INC.
New York 23, New York


reduce
calls
on the
blood
bank..

Adrenosem®*

Salicylate

(brand of carbazochrome salicylate)

Adrenosem helps conserve a patient's own blood. Adrenosem has become accepted pre-op medication because it minimizes the need for transfusion.

Research[1,2] has shown that lack of capillary integrity causes abnormal bleeding four times as often as do coagulation defects. Adrenosem maintains capillary integrity by decreasing excessive capillary permeability while it also promotes retraction of severed ends.

Besides reducing need for transfusion, Adrenosem's control of bleeding results in a clearer operative field . . . makes good technic even better. Adrenosem also lessens the hazard of serious postoperative bleeding . . . reduces ooze and seepage.

Adrenosem is indicated pre- and postoperatively in surgery and also nonsurgically to control bleeding associated with vascular pathosis as in peptic ulcer, telangiectasia, purpura, ecchymosis, ulcerative colitis, and others.

There are no contraindications to Adrenosem at recommended dosage levels.

supplied: For I. M. injection only—Ampuls: 5 mg. (1 cc.) and 10 mg. (2 cc.). For oral administration—Syrup: 2.5 mg./5 cc. (1 tsp.); Tablets: 1 and 2.5 mg.

references: 1. Haden, R. L., et al.: Ann. N.Y. Acad. Sc. 49:641 (May 11) 1948. 2. Cheraskin, E.: J. Am. Dent. Assn. 58:17 (April) 1959.

*U.S. Pat. Nos. 2581850; 2506294

WRITE FOR DETAILED LITERATURE
AND DOSAGE INFORMATION

THE S. E. MASSENGILL COMPANY

Bristol, Tennessee

New York • Kansas City • San Francisco

If you were treating 25 pregnant, habitual aborters right now, what rate of success could you anticipate?

Lipp[1] administered DEPO-PROVERA to 25 pregnant, habitual aborters who totalled 94 previous successive abortions. Each patient had been under medical treatment for 8 to 48 months. DEPO-PROVERA was started between the third and eighth weeks of pregnancy. Six patients received an average of 5.7 injections of 25 mg. through the twentieth week, and 19 received an average of 4.4 injections of 50 mg. during the same period of time.

The results: The first group of 6 patients delivered 4 viable infants (67% salvage) while the second group of 19 patients delivered 16 (84% salvage). No side effects occurred and there was no evidence of female fetal masculinization.

Consider Intramuscular DEPO-PROVERA and Oral PROVERA for habitual aborters in your own practice: □ *in parenteral form—a single 50 mg. injection produces a progestational effect for up to 16 days.* □ *in oral form—effective action with small oral dose.* □ *no significant side effects reported during extensive clinical study.*

1. Lipp, R.G.: Habitual Abortion—Treatment with Parenteral Medroxyprogesterone Acetate, to be published.

Upjohn

Brief Basic Information

	Description	Indications	Dosage: Threatened abortion	Dosage: Habitual abortion	Supplied	Precautions
Oral Provera*	Upjohn brand of medroxyprogesterone acetate.	Threatened and habitual abortion, infertility, secondary amenorrhea, functional uterine bleeding.	10 to 30 mg. daily until acute symptoms subside.	1st trim. 10 mg. daily 2nd trim. 20 mg. daily 3rd trim. 40 mg. daily, through 8th month.	2.5 mg. scored, pink tablets, bottles of 25; 10 mg scored white tablets, bottles of 25 and 100.	Clinically, Provera is well tolerated. No significant untoward effects have been reported. Animal studies show that Provera possesses adrenocorticoid-like activity. While such adrenocorticoid action has not been observed in human subjects, patients receiving large doses of Provera continuously for prolonged periods should be observed closely. Likewise, large doses of Provera have been found to produce some instances of female fetal masculinization in animals. Although this has not occurred in human beings, the possibility of such an effect, particularly with large doses over a long period of time, should be considered. Provera, administered alone or in combination with estrogens, should not be employed in patients with abnormal uterine bleeding until a definite diagnosis has been established and the possibility of genital malignancy has been eliminated.
I. M. Depo-Provera*	Each cc. contains: Medroxyprogesterone acetate, 50 mg., Polyethylene glycol 4000, 28.8 mg. Polysorbate 80, 1.92 mg., Sodium chloride, 8.65 mg., Methylparaben, 1.73 mg., Propylparaben, 0.19 mg.; Water for injection, q.s.	Threatened and habitual abortion.	50 mg. I.M. daily while symptoms are present, followed by 50 mg. weekly through 1st trimester or until fetal viability is evident.	1st trim. 50 mg. I.M. weekly 2nd trim. 100 mg. I.M. q. 2 wks. 3rd trim. 100 mg. I.M. q. 2 wks. through 8th month.	Sterile aqueous suspension for intramuscular use only, 50 mg. per cc., in 1 cc. and 5 cc. vials.	

*Trademark, Reg. U.S. Pat. Off.

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80%
fetal salvage
in 25
habitual
aborters
with
94 previous,
successive
abortions[1]

Intramuscular **Depo-Provera**

Oral Provera





"the pill"...so

...some timely comments

***Ovulation is inhibited during cyclic therapy with* ENOVID.** This single fact has made conception control by oral means a reality. As Guttmacher[1] states, oral therapy with ENOVID "is the best, the most effective contraceptive known to man. Its failure rate in patients who take it consistently is virtually zero."

Therefore, a physician's decision to prescribe ENOVID for conception control is likely to be influenced by considerations other than lack of faith in its *dependability*.

ENOVID is easy to take, economical and effective. But more important to the physician and the woman is the possibility of long-term undesirable effects.

Conception control by oral means deserves to be viewed with healthy scientific skepticism. "No method[2] of pregnancy spacing, even though highly effective, is justifiable if it endangers life or health." In the case of ENOVID, overwhelming evidence has been accumulated to establish not only its efficacy—but its *singular safety*.

The effects of ENOVID have now been studied in more than 3,500 women during more than 49,500 menstrual cycles, representing 3,800 woman-years of experience. ENOVID has been administered *cyclically* to the same patients for as long as five and one-half years for ovulation inhibition, and in other patients it has been administered *continuously* for more than a year in the treatment of endometriosis. *No true toxicity or contraindication to* ENOVID *therapy has been observed.*

There has been no impairment of subsequent fertility. ENOVID produced no masculinization or other harmful effect on the fetus when given to women who had already conceived. Although a cautious limit of two years is presently set for cyclic therapy with ENOVID, it is expected that this period will be lengthened as experience continues to accumulate.

ENOVID is available in tablets of 5 mg. and of 10 mg. Available on request: literature and references covering more than six years of intensive clinical study.

1. Guttmacher, A. F. (Chairman and Moderator): Clinical Experience with and Practical Techniques for the Use of Enovid in Ovulation Control, Transcript of a Closed Circuit Television Symposium, Chicago, G. D. Searle & Co., Jan. 18, 1961, pp. 26-28.

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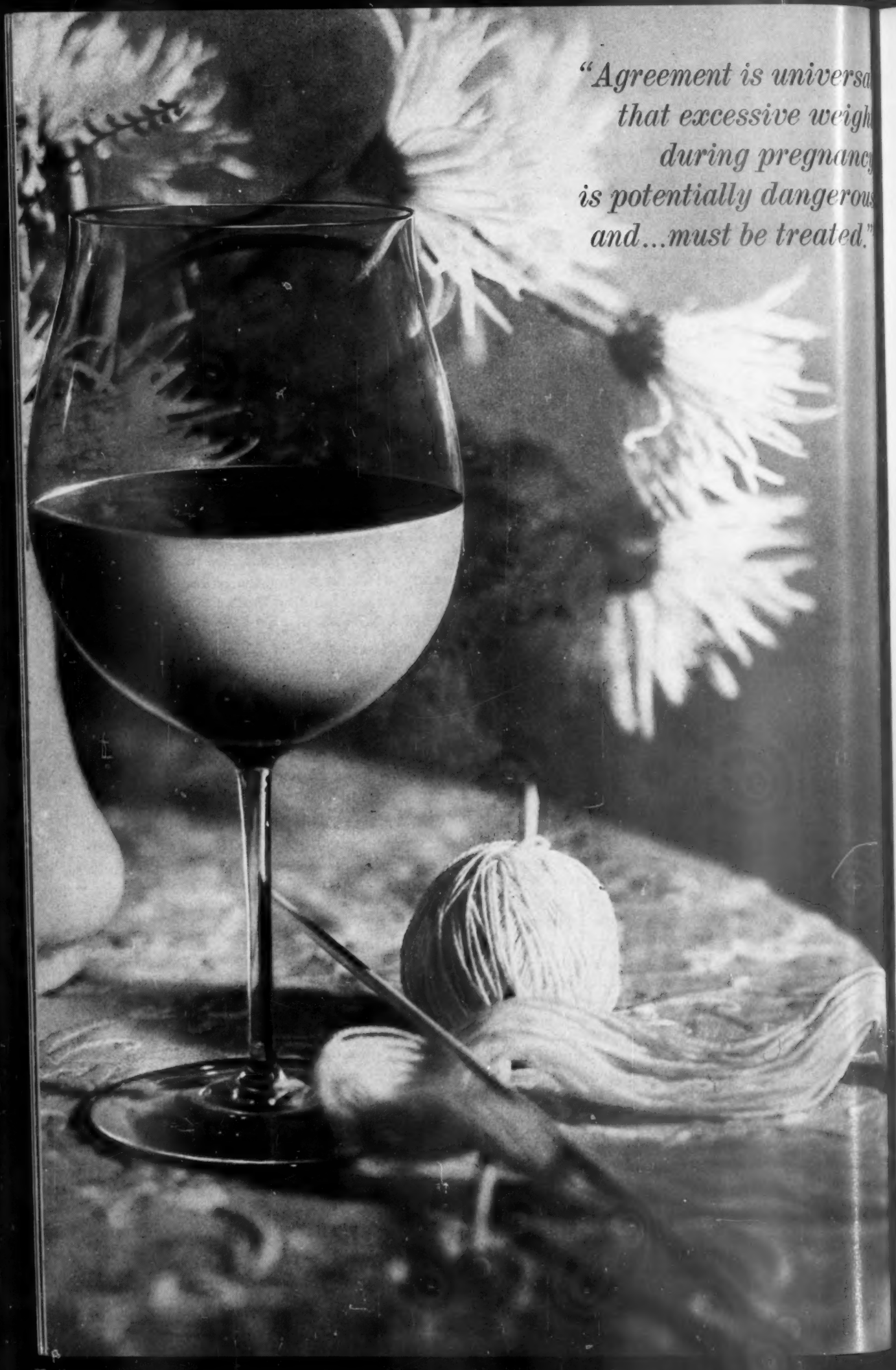
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"Agreement is universa
that excessive weigh
during pregnanc
is potentially dangerou
and...must be treated."

during the childbearing years

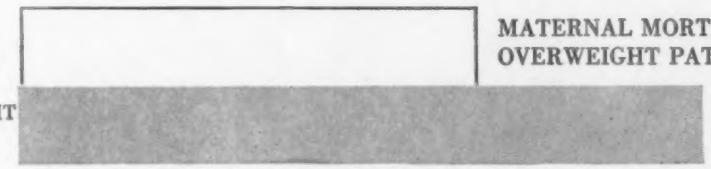
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BRAND DIETARY FOR WEIGHT CONTROL

IN THE MANAGEMENT OF OBESITY
DURING PREGNANCY, POSTPARTUM, BETWEEN PREGNANCIES

"The patient should be encouraged to adopt a good nutrition program at the beginning of pregnancy, to maintain it throughout lactation, and, with appropriate adjustments, to continue it during the intervals between pregnancies."[2]

The dietary care of the obstetric patient requires careful consideration to help avert serious complications. Obese patients present a special problem to the physician.



†One per every 2,700 live births[3] *Adapted from Sands, R. X.[1]

In addition to the high mortality (150 per cent of expected rate), "Overweight patients had a greater frequency of pre-eclampsia and stillborn children...."[2] The obese pregnant woman has an increased incidence of uterine inertia, prolonged labor, postpartum hemorrhage, anemia, oversized infants, and runs a greater surgical or anesthetic risk than women of normal weight.[1]

Highly Flexible...

Metrecal can provide the basis for a complete low-calorie diet.[4] According to the indication, Metrecal may be used for one or two meals a day or as the total diet two or three days a week, for controlling weight during pregnancy, for losing weight postpartum, and for preventing additional weight gain between pregnancies.[5]

Composition Facilitates Dietary Management

The 900-calorie daily allotment of Metrecal provides:

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Protein	70 Gm.
Fat (6.3 Gm. saturated; 13.7 Gm. unsaturated)	20 Gm.
Carbohydrate	110 Gm.
Iron	15 mg.
Calcium	2 Gm.
Vitamin D	400 units
Sodium	0.9 Gm.

Plus other essential vitamins and minerals.

NEW—Metrecal Wafers: All the advantages of Metrecal plus the satisfaction of solid food.

References: (1) Sands, R. X.: Obst. & Gynec. *16*:605-609 (Nov.) 1960. (2) Hillman, R. W., in Wohl, M. G., and Goodhart, R. S.: Modern Nutrition in Health and Disease, ed. 2, Philadelphia, Lea & Febiger, 1960, pp. 963, 968. (3) Monthly Vital Statistics Report, Annual Summary for 1959, U.S. Dept. Health, Education, and Welfare, Aug. 12, 1960. (4) Tullis, I. F.; Allen, C. E., and Overman, R. R.: Simple Effective Weight Reduction: A Clinical Study, Scientific Exhibit, 6th Internat. Cong. Int. Med., Basel, Switzerland, Aug. 24-27, 1960. (5) Edward Dalton Co.: Unpublished data. 68561

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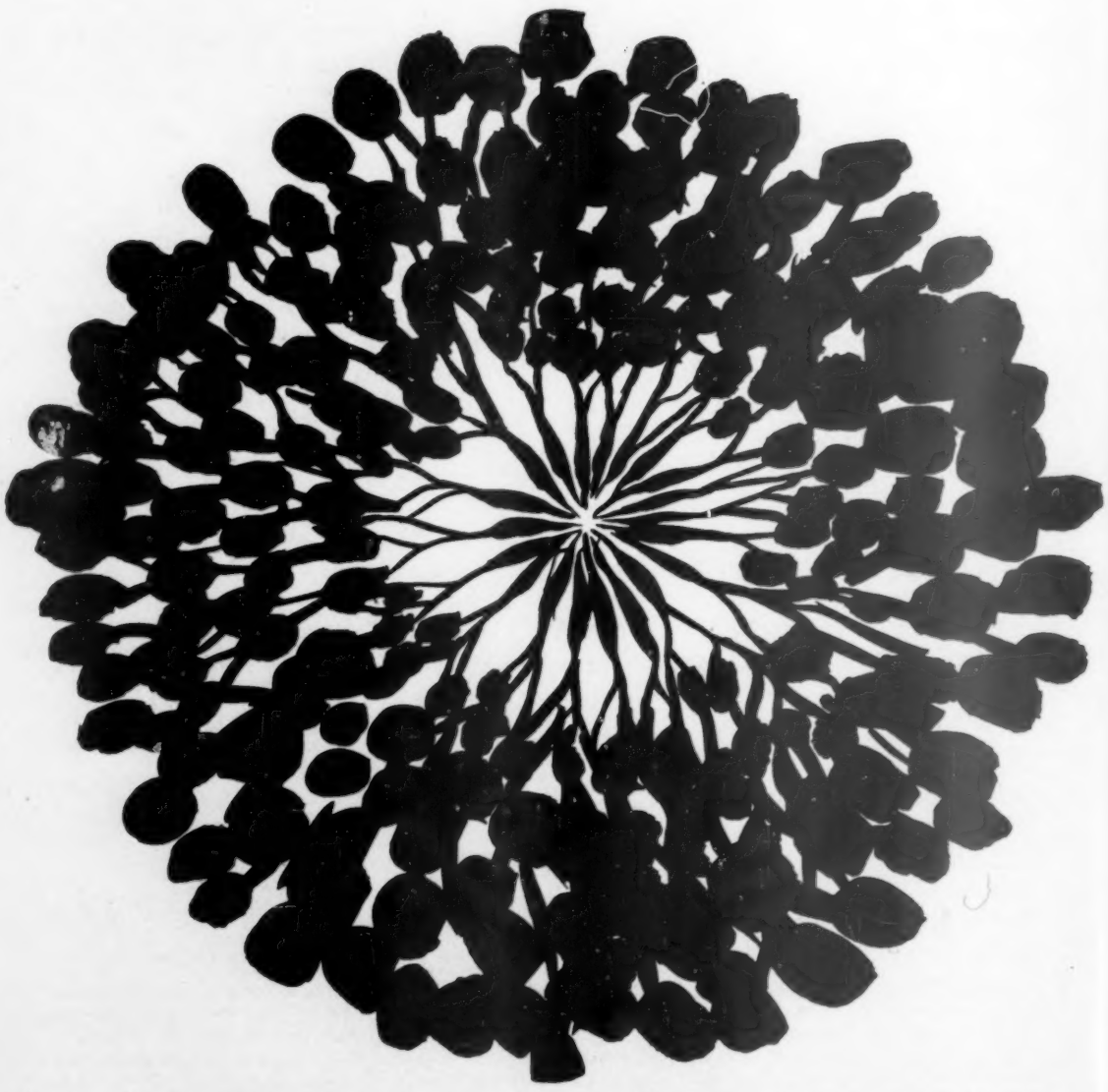
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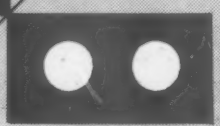
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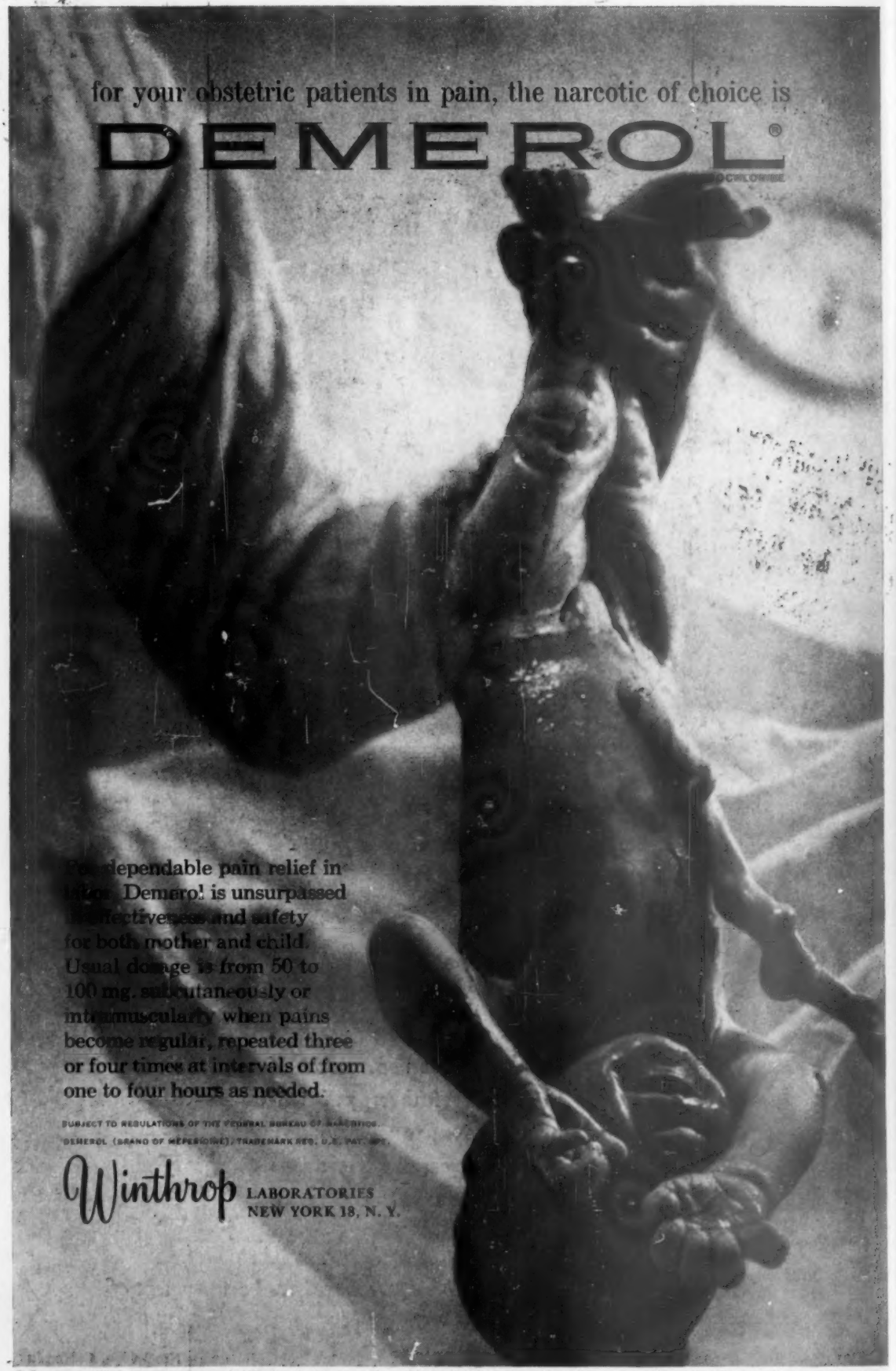
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